Diagnosis and Management of Epithelial Ovarian Cancer

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Contents

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Abstract

Ovarian cancer is the fifth most common cancer among women after breast, bowel, lung, and endometrial and remains the leading cause of death due to gynecological malignancy (Cancer.org 2016). Epithelial ovarian cancer accounts for the vast majority of ovarian malignancies with figures of around 85 %. Due to its insidious nature of presentation, it is often not diagnosed until the later stages leading to a high mortality rate. Five-year survival is very much influenced by stage at diagnosis. Over the last 20 years, incidence and mortality have remained fairly static, and much research is being undertaken looking for aids to diagnosis, possible screening methods, and improvement in treatment options, both surgical and medical. In this chapter we will discuss presentation, diagnostic tools, and possible management regimes for patients with epithelial ovarian cancer.

Keywords

Epithelial • Diagnosis • Imaging • Staging • Management

1 Introduction

Epithelial ovarian cancer (EOC) is the second most common genital malignancy after uterine cancer in women and accounts for the majority of deaths from gynecological malignancies in Western countries (Jemal et al. 2007). Lifetime risk is about 1.6 %; the latest data show that 1 in 43 women will develop EOC during their lifetime. Women with a mutated BRCA1 or BRCA2 gene are at increased risk ranging between 25 % and 60 % depending on the specific mutation.

Despite the continuous advances in diagnostics and imaging, more than 70 % of the patients with newly diagnosed EOC will present with an advanced stage FIGO III and IV. This is mainly attributed to the unusual tumor biology and clinical behavior of the disease, which is typically associated with locoregional dissemination throughout the peritoneal cavity. This behavior results in a delay of symptoms until only at a later stage in a rather nonspecific pattern, including abdominal bloating and distention with pain, urinary frequency, postmenopausal bleeding, loss of appetite, and occasionally rectal bleeding (Goff 2012). This unusual natural history has therefore generated unique therapeutic strategies that highlight the important contribution of locoregional control to survival for this disease (Vaughn et al. 2011).

The last decades have brought a significant advance in the treatment of EOC, both in surgical and systemic aspects, with the development and addition to standard treatment of extensive cytoreductive techniques, refinement of surgical skills in the upper abdomen, dose-dense regimes, and novel targeted therapies. Nevertheless, the survival rate of women with EOC has changed little since the revolutionary platinum-based treatment that was introduced more than 30 years ago (Omura 1986).

Only in the recent years, targeted therapies based on the principle of antiangiogenesis (Monk 2009) and homologous recombination repair mechanisms have brought a significant efficacy in the treatment of EOC: bevacizumab, pazopanib, and olaparib have proven in a maintenance regime during and/or after successful chemotherapy their efficacy in significantly prolonging progression-free survival (PFS), but failed to significantly influence the overall survival of the patients (Janczar et al. 2009). A possible mechanism discussed for this consistent discrepancy is the high rate of crossover in the subsequent lines that contaminate any survival benefit attributed to each agent.

Great changes in the way we understand ovarian cancers have occurred in the last decade. Traditionally ovarian cancers have been categorized based on their origin either from mesothelial epithelial cells, germ cells, or stromal cells, this being based on the theory that epithelial ovarian cancers arise from the ovarian epithelium. However it is now widely believed that high-grade serous ovarian cancers more likely arise from the epithelium of the fallopian tubes and ovarian deposits are therefore secondary implants. As such these are

now investigated and managed as a group with primary peritoneal carcinomas (Kurman et al. 2010). Epithelial ovarian malignancies are histologically divided into serous carcinoma, mucinous carcinoma, endometrioid carcinoma, undifferentiated carcinoma, and clear cell carcinoma. These are further divided into low-grade and high-grade subtypes with low grade tending to be more stable and high grade behaving aggressively and usually presenting at an advanced stage (Doufekas 2014).

Management and prognosis are determined by stage at presentation and histological grading following biopsy or debulking surgery. The etiology of epithelial ovarian cancers has been studied at length. Factors found to increase risk include age, with most diagnoses made after 40 years, a steep curve after 50, and peak in the 80s. Around 10 % of ovarian cancers have a hereditary component with the vast majority being BRCA1 and two mutations; there is also an association with hereditary non-polyposis colorectal cancer. Previous breast cancer, nulliparity, history of endometriosis, and long-term use of hormone replacement therapy have also all been shown to increase risk of ovarian cancer. Conversely, prolonged use of combined oral contraceptive medication, parity, and breastfeeding have been associated with risk reduction as well as history of tubal ligation and hysterectomy. Recent evidence even suggests that women who give birth to their first child in their mid-30s or later may have an even lower risk of ovarian cancer compared to those who gave birth to their first child earlier than that. Each 5-year increase in a woman's age at birth of their first child seems to correspond to a 16 % lower risk of ovarian cancer. This association is not fully understood; however a possible mechanism is a progesterone-mediated effect which seems to be more prevalent and efficient in older women.

2 Presentation

Ovarian cancer often presents at a late stage and can be difficult to diagnose. This is because the signs and symptoms tend to be nonspecific and are sometimes put down to gastrointestinal upset. Common symptoms include bloating, loss of appetite, abdominal pain, disturbance in urinary or bowel habit, and weight loss. Patients may have increased abdominal girth, evidence of pelvic mass and ascites, bowel obstruction, and, depending on stage of presentation, a cachectic appearance.

Correct diagnosis is often delayed either because patients do not present to a medical professional or due to initial misdiagnosis of conditions such as irritable bowel disease, diverticular disease, and urinary tract infection.

3 Diagnosis

3.1 History and Assessment

If a diagnosis of ovarian cancer is suspected, a referral should be made to a specialist gynecological oncology center.

In clinic a full history should be taken including symptoms, age, parity, past medical history, and past surgical and gynecological history, especially focusing on risk factors, e.g., previous endometriosis or malignancies. Although the majority of patients will present postmenopausal, it is important to determine a patients' wishes with regard to fertility if premenopausal as this may influence management. Past surgical history is important as most treatment options for epithelial ovarian cancer will involve surgery and previous abdominal operations could complicate this. Different options for management will also be determined by the patients' performance status; therefore a full medical history is important to include, e.g., history of diabetes, respiratory or cardiac diseases, and smoking status. Social history should include who their support system is (family/friends), given the gravity of potential diagnosis being made. It will also contribute to the assessment of a patient's performance status; for example, someone requiring nursing home care will likely be a more complex surgical candidate than someone who is independent and living in their own home. Fragility scores predicting

surgical outcome in older patients with comorbidities have not been well defined in ovarian cancer surgery; it is however the focus of various currently ongoing studies.

Examination in clinic should include patients' BMI, blood pressure, and heart rate. These simple observations will help indicate their current health status. Abdominal examination should assess for distension, presence of a mass or ascites, any tenderness, and previous scars. Vaginal examination will help with assessment of size and mobility of a pelvic mass, an indication of the likely difficulty of surgery. Rectal examination is helpful in determining any invasion of disease and to help instruct if rectal resection is likely to be necessary.

4 Bloods

Initial blood tests should include baseline full blood count, renal, and liver function and tumor markers to help determine the origin of the cancer. Markers should be sent for cancer antigen 125 (Ca125) for ovarian pathology, carcinoembryonic antigen (CEA) for colorectal, carbohydrate antigen 19-9 (Ca 19-9) for pancreatic/gastrointestinal malignancies, and possibly alpha-fetoprotein if germ cell tumor is suspected. Ca 125 has a low sensitivity of 55 % as it can be raised due to many processes in the pelvis, usually inflammation from infection or endometriosis. The ration of CA125 to CA199 could indicate a non-ovarian pathology and dictate the necessity of further investigations like colonoscopy. Some epithelial ovarian cancers will not express Ca125 and this makes them more difficult to follow-up posttreatment.

5 Imaging

Transvaginal ultrasound is the most commonly used modality for first-line imaging in epithelial ovarian cancer. It can demonstrate the presence of pelvic mass and the characteristics of the mass. It can also detect any free fluid in the pelvis and assess if the adnexal structures are fixed or mobile indicating the possible presence of adhesions. Features suggestive of malignancy include a multilocular mass, presence of papillary structures, solid areas, and a mass with increased vascularity on Doppler ultrasound. Risk of malignancy index can be used to help assess the likelihood of a mass being malignant. This is done by a simple calculation of a score given to the ultrasound findings, the menopausal status of the patient, and the Ca125 level (NICE 2011). The International Ovarian Tumor Analysis (IOTA) guidance may be used for premenopausal women (Timmerman 2010). Simple rules were applicable in 77 % of adnexal masses and when inconclusive masses were considered as malignant, reporting a sensitivity of 91 % and specificity of 93 %. Guidance could consider supporting recruitment into ongoing trials that evaluate diagnostic tests and presurgical triage.

Magnetic resonance imaging (MRI) of the pelvis is used to correlate with USS to help further determine the nature of a mass in patients with the absence of metastatic sites and with fertility sparing wish, for additional guidance in regard to whether such an approach would be advisable or feasible.

Computerized tomography (CT) is used to evaluate stage and tumor dissemination pattern of the disease and especially identify distant intraparenchymatous metastases that would determine operability and course of optimal therapeutic approach. Additionally, chest pathology like pulmonary embolism, mediastinal lymphadenopathy, etc., can be identified and have impact on therapeutic decisions.

Epithelial ovarian cancer acts like a rash within the abdomen using the peritoneum as a vector; the disease is most commonly seen on the peritoneum covering the pelvis, bladder, para-colic areas, upper abdominal structures, and diaphragm. Omental disease can occur in deposits or forming one large "cake" of disease. Para-aortic and pelvic lymph nodes may be enlarged. CT can assess the presence of disease on the splenic surface and liver capsule plus any deposits on small/large

bowel serosa, mesentery, and any more invasive lesions that may require a bowel resection to remove. CT PET (positron emission tomography) scans use a radioactive glucose solution which is injected into patients and the uptake monitored. The glucose solution is more readily taken up by cancerous cells, and therefore this imaging modality is useful in helping to locate areas of metastasis and also disease activity in lymph nodes. The rate of uptake can also advise on the potential grade of the cancer.

6 Pathology

Examination, blood results, and imaging may be sufficient to provide a working diagnosis of ovarian cancer, and even though histological diagnosis prior to primary surgery is not mandatory, it would be advisable to be available in borderline cases with atypical clinical pattern, in young women with fertility sparing wish – in which case a two-stage approach should be followed. If ascites is present, this can be drained and samples sent for both cytology and microscopy. Biopsies may be taken from tumor deposits demonstrated on imaging on the peritoneum or omentum or sometimes from the mass itself; this is usually done under USS or CT guidance. Occasionally the histology is already known from previous surgery such as an oophorectomy for ovarian cyst at another unit, and the patient is then referred to the specialist unit for ongoing management. If a CT- or US-guided biopsy is not technically possible, then a laparoscopic histological confirmation should be performed.

7 Staging

Using the imaging a provisional staging can be made. It should be noted that full staging will come after surgery, if this takes place, once the suspicious tissues have been removed and examined histologically. Imaging may indicate affected areas which turn out to be benign after excision and vice versa.

The staging for ovarian cancer as per FIGO 2014 is as follows (Helm 2014)	
Stage I consists of tumor limited to the ovaries or fallopian tubes	
Stage IA includes the following	
Tumor limited to one ovary (capsule intact) or fallopian tube	
No tumor on the external surface of the ovary or fallopian tube	
No malignant cells in ascites or peritoneal washings	
Stage IB includes the following	
Tumor limited to both ovaries (capsules intact) or fallopian tubes	
No tumor on the external surface of the ovaries or fallopian tubes	
No malignant cells in ascites or peritoneal washings	
Stage IC includes tumor limited to one or both ovaries or fallopian tubes, with any of the following:	
Stage IC1	Surgical spill
Stage IC2	Capsule ruptured before surgery, or tumor on ovarian or fallopian tube surface
Stage IC3	Malignant cells in the ascites or peritoneal washings
Stage II tumor involves one or both ovaries or fallopian tubes, with pelvic extension (below pelvic brim) or primary peritoneal cancer	
Stage IIA	Extension and/or implants on the uterus and/or ovaries and/or fallopian tubes
Stage IIB	Extension to other pelvic intraperitoneal tissues
Stage III tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
Stage IIIA1	Positive (cytologically or histologically proven) retroperitoneal lymph nodes only
Stage IIIA1(i)	Metastasis up to 10 mm in greatest dimension
Stage IIIA1(ii)	Metastasis more than 10 mm in greatest dimension
Stage IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
Stage IIIB involves macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	
Stage IIIC involves macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes. Stage IIIC includes extension of tumor to the capsule of liver and spleen without parenchymal involvement of either organ	

(*continued*)

Stage IV
Stage IV consists of distant metastasis, excluding peritoneal metastases, and includes the following:
Stage IVA: Pleural effusion with positive cytology
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

8 Management

Treatment of epithelial ovarian cancer is from a multidisciplinary approach based on input from expert gynecological oncologists, medical oncologists, pathologists, and radiologists. In comprehensive cancer centers, patients should ideally be additionally supported by a specialist nurse to help them with their treatment journey (Vernooji 2007). The mainstay of treatment is surgical cytoreduction combined with systemic agents.

9 Definition of Surgery in EOC

The large differences in current practice nationally and internationally are also being reflected in the discrepancy in the terminology used to adequately characterize the different types of surgery at the different stages of the disease. A clarification of the various definitions used broadly is necessary before proceeding so that the context is clear:

- Exploratory surgery: usually laparoscopically to assess intraperitoneal dissemination patterns; the value of this in assessing operability is highly questionable and not standard practice, unless to set histological diagnosis or in cases of unclear ascites with absent ovarian mass or peritoneal disease at imaging.
- Primary or upfront cytoreduction: tumor debulking at initial diagnosis before any systemic treatment, aiming at maximal tumor reduction and ideally total macroscopic tumor clearance.
- Interval debulking: cytoreductive surgery after usually three cycles of neoadjuvant chemotherapy.
- Second look surgery: exploratory laparotomy or laparoscopy after completion of systemic treatment to confirm response; this method is obsolete, since it has no evidence of survival benefit.
- Secondary surgery: surgery due to the first relapse. Here definition is unclear in regard to aim; usually used to describe cytoreductive effort but can also be used for palliative surgery due to symptoms at first relapse.
- Tertiary surgery: the equivalent of secondary surgery at the second relapse.
- Quaternary surgery: the equivalent of secondary surgery at the third relapse.
- Palliative surgery: surgery aiming at palliation of tumor-induced symptoms, such as bowel obstruction and intestinal perforation, where conservative management has failed.

The maximum diameter of the postoperative residual tumor after cytoreductive surgery is considered the strongest independent clinical prognostic factor (Du Bois et al. 2009). Bristow et al. published for the first time a systematic meta-analysis on this subject based on a total of 53 studies with 6885 patients overall (period: 1989–1998).

They studied the influence of surgical tumor resection on overall survival. Published studies with surgically operated patients with FIGO stage III or IV and subsequent platinum-based chemotherapy were evaluated. According to this meta-analysis, patient cohorts that had had a maximum tumor reduction rate (<2 cm) of over 75 % had a median overall survival of 36.8 months. By contrast, patient cohorts with a maximum tumor reduction rate of less than 25 % had a median overall survival of only 23 months. Every 10 % reduction in tumor was associated with a 6.3 % prolongation of median overall survival (Bristow et al. 2002).

There is internationally ongoing debate as to the best timing of surgery, whether this should be done at the outset of treatment or following a course of neoadjuvant chemotherapy. However, the general recommended course of treatment for those patients with good performance status and resectable disease is primary debulking surgery

followed by adjuvant chemotherapy (Colombo et al. 2009). Neoadjuvant chemotherapy can be used if the extent of the disease at the time of presentation is deemed to be not suitable for surgical resection; the patient is not fit enough to undergo a primary debulking due to advanced age, low performance status, and comorbidities, or for bridging acute events like thromboembolic episodes. Nevertheless, practice regarding the optimal upfront approach varies strongly between centers and countries and often depends on the gynecological oncology center and experience of surgeon. Two prospective randomized trials (Vergote et al. 2010; Kehoe et al. 2015) have demonstrated lower surgical morbidity and mortality in the neoadjuvant approach; however the oncologic safety is being doubted since both trials included mainly patients who had undergone in their majority suboptimal cytoreduction with much lower resection rates then anticipated in specialized centers for the disease. For that reason, future prospective randomized trials with strictly defined surgical quality are warranted in order to answer this question and establish optimal practice. These future trials will address additional issues such as management of fragile patients, assessment of short- and long-term quality of life scores, impact of ascites, and pleura effusion on hemodynamic management and would also have an additional translational portfolio in an attempt to identify valid biomarkers that would predict operability and clinical outcome. These are often extensive operations with the possibility of large volume shifts. Therefore, anesthetic involvement prior to proceeding is recommended and an ITU bed may be indicated. Surgery for ovarian cancer should always ideally be carried out by an experienced gynecological oncology surgeon (Eisenkop 1992; Paulsen 2006).

10 Tumor Dissemination Patterns at Relapse

A better understanding of the tumor dissemination patterns followed in the primary and subsequently in the recurrent situation of EOC is highly essential for the better understanding of the disease and may enhance the evolution and refinement of surgical and, by extension, systemic approach (Gabra 2010). Nevertheless, data correlating the tumor dissemination pattern and surgical outcome in primary and later recurrent situation at the same patient hardly exist. A prospectively maintained database evaluating the intraoperative tumor dissemination pattern and operative outcome of all women who underwent both primary and secondary tumor-debulking surgeries in the same institution within a 10-year period of time has been systematically analyzed (Braicu 2011). On the basis of 79 patients, it could be demonstrated that secondary cytoreduction appears to be associated with significantly lower optimal tumor-debulking rates compared to primary debulking, mainly attributed to less "accessible" recurring patterns such as gastrointestinal serosa, radix mesenterii, gastric serosa, and porta hepatis. Interestingly, no significant predictors of surgical outcome or tumor pattern, such as peritoneal carcinomatosis, intestinal tumor involvement, or positive lymph nodes, could be identified between primary and relapse. It appeared that a different tumor "behavior" is followed in the primary compared to recurrent situation of the disease even in the same patient, while interestingly the primary tumor patterns do not appear to have any predictive value for the tumor patterns at recurrence, apart from the predictive value of initial tumor residuals which clearly correlate with the amount of postoperative tumor residuals at relapse. Venturing even beyond surgical borders, one could say that ovarian cancer reappears under a different dissemination profile than at its initial presentation in terms of a higher "aggressivity" and higher dissemination tendency. Any potential attempts to derive clinically relevant conclusions on the outcome of the forthcoming cytoreduction depending on the outcome and tumor dissemination at the outset of the disease would rather fail. Therefore, novel biomarkers are warranted in order to predict tumor patterns followed at recurrence and hence surgical outcome.

The role of imaging is also unclear in the characterization of peritoneal carcinosis as definite basis for indication for surgery at relapse, even though PET-CT appears to have higher

accuracy indices than simple CT. Results suggest that PET/CT may prove a useful tool for presurgical staging of ovarian cancer with a sensitivity and specificity of 78 % and 68 %, respectively. In a prospective trial correlating the PET-CT results with laparoscopic findings, PET/CT showed an adequate correlation between SUVmax values and laparoscopy findings of lesions >5 mm, but a high rate of false negative results in lesions <5 mm such as in carcinomatosis (De Iaco 2010). Clinical decision-making processes should therefore be very carefully constructed around clinical findings and symptoms and history of the disease and not on imaging alone.

Interestingly, it appears that patterns of relapse may also be altered depending on the primary mode of treatment. In a retrospective evaluation of 175 stage IIIC-IV EOC patients who were operated in an Italian gynecology cancer center with diffuse peritoneal carcinosis, patterns of relapse were stratified according to whether the patient had upfront or interval debulking surgery at initial presentation (Petrillo et al. 2013). Forty patients received complete primary debulking surgery, and the remaining 135 were treated with neoadjuvant chemotherapy followed by interval debulking surgery with absent residual tumor after surgery. No differences were observed in the distribution of clinical pathological characteristics at the time of diagnosis between the two groups. In a median follow-up period of 31 months (range 9–150 months), the authors observed 20 (50.0 %) recurrences in the upfront group compared to 103 (76.3 %) in the interval debulking group. Duration of primary platinum-free interval was also significantly shorter in the interval debulking arm (13 vs. 21 months, respectively). A significantly higher percentage of patients in the interval debulking group experienced platinum-resistant recurrences and carcinomatosis at the time of relapse. Also the platinum-free interval of second relapse was significantly longer in favor of the upfront arm. This documented more "favorable behavior" of recurrent disease in EOC patients with diffuse peritoneal carcinomatosis treated with complete upfront surgical approach compared to women submitted to neoadjuvant chemotherapy needs to be prospectively validated in larger datasets; however it does give a clear signal about the highly significant impact of the quality of upfront treatment even in peritoneal disseminated disease.

11 Value of Secondary Cytoreduction

There is clear evidence that patients experiencing an early platinum resistant or even refractory EOC relapse are highly unlikely to benefit from secondary debulking surgery. Older reports could demonstrate very dismal overall survival rates of a mean value of 8 months, not adequately justifying a radical surgical approach but rather concentrating on palliation (Morris et al. 1989; Segna 1993). Anecdotal and empirical case reports may demonstrate a survival benefit in platinum-resistant patients who present with early lymph node relapse which rather represents a persistent lymph node metastasis not removed through lymph node dissection at primary surgery and hence not representing a true relapse (Chan 2007). The selection of these patients however is very challenging and no randomized data will ever exist for this special subgroup of women. Caution should be awarded to adequately judge and evaluate situations always taking into consideration the quality of surgery at primary or interval debulk and the tumor dissemination pattern at relapse.

The first systematic data analysis for secondary debulking in a platinum-sensitive setting originates from the German AGO (Arbeitsgemeinschaft Gynaekologische Onkologie) within the DESKTOP I trial (Harter et al. 2006). This was a retrospective evaluation of 267 patients which showed that patients appeared to benefit from surgery in recurrent EOC only when total macroscopic clearance was achieved. Complete tumor resection was associated with significantly longer survival compared with surgery leaving any postoperative residuals. Hence, the challenge was to accurately preoperatively identify the optimal candidates for surgery, in order to avoid surgical procedures that would not have a prognosis

benefit for the patients. Based on a multivariate model, three factors were identified as independently predicting resectability, building so the so-called AGO score: good performance status, complete resection at primary surgery, and absence of ascites. The value of the AGO score lies with others also in the simplicity to use, based on easy-to-assess clinical features and not on complicated mathematic algorithms that would make its use in the daily routine very challenging. An exploratory analysis of the DESKTOP results to evaluate the role of peritoneal carcinomatosis present in recurrent EOC clearly showed that even though peritoneal carcinomatosis was a negative predictor for complete resection in the recurrent situation of the disease, it appeared to have no negative impact on survival if total macroscopic clearance could be achieved. The authors concluded that improving surgical skills might increase the patient proportion that could benefit from surgery for recurrent disease (Harter et al. 2009).

A subsequent confirmation and validation of the AGO score followed within the prospective, multicenter DESKTOP II trial, in which the AGO score could be confirmed as a useful and reliable tool to predict complete tumor resection in more than two thirds of patients with platinum-sensitive relapsed EOC (Harter et al. 2011). Participating centers prospectively enrolled patients with platinum-sensitive first or second relapse. The AGO score was then applied to all patients, but each center was free to decide the therapeutic management. A total of 516 patients were screened within 19 months; of these, 261 patients (51 %) were classified as score positive, and 129 patients with a positive score and first relapse received a secondary tumor debulking. The rate of complete resection was 76 %, thus confirming the validity of this score regarding positive prediction of complete resectability in more than two thirds of patients. Interestingly on analysis poor correlation of imaging and intraoperative findings was found, both in terms of number of lesions identified and localization of tumor.

Perioperative morbidity and mortality appeared to be acceptable within the DESKTOP series with a mortality as low as 0.8 % and an 11 % relaparotomy rate mainly due to bowel leakage or fistula (7 %). DVT rate was 2 %, while 52 % of the patients required a postoperative intensive care stay of a median 2 days (range: 1–20). Morbidity and mortality data of other equivalent series are in a similar level.

A subsequent multicenter randomized trial, the DESKTOP III (AGO-Ovar OP.4.), commenced in June 2010, to prospectively evaluate the impact of recurrent EOC-surgery in platinum-sensitive patients with positive AGO score (tumor-free initial surgery, good performance status, and ascites $<$500 ml). The study has completed recruiting all 409 preplanned patients and results are now awaited within the next 2–3 years. This very important study is anticipated to finally answer the question whether surgery at the relapse situation of the disease is truly associated with a benefit for survival and quality of life of the affected patients.

The equivalent American trial from the GOG (GOG 0213) has been recruiting for a longer period than the DESKTOP trial, however in a slower rhythm. A further difference is the additional randomization to systemic bevacizumab 15 mg/m^2 at maintenance. There are future plans to combine data of both trials together to achieve a larger cohort and more robust survival data.

The largest retrospective multicenter and multinational analysis worldwide showed equivalent results (Zang et al. 2011; Tian et al. 2012). Of the 1075 evaluated patients, 434 (40.4 %) underwent complete resection. Total macroscopic tumor clearance was associated with a significant improvement in survival, from a median OS of 57.7 months, when compared with only 27.0 months in those with residual disease of 0.1–1 cm and 15.6 months in those with residual disease of $>$1 cm, respectively. Complete secondary cytoreduction was associated with six variables: FIGO stage, residual disease after primary cytoreduction, PFS, Eastern Cooperative Oncology Group (ECOG) performance status, CA125, and ascites at recurrence. These variables were entered into the risk model and assigned scores ranging from 0 to 11.9. Patients with total scores of 0–4.7 were categorized as the low-risk group, in which the proportion of complete cytoreduction

was 53.4 % compared with 20.1 % in the high-risk group. In external validation, the sensitivity and specificity was 83.3 % and 57.6 %, respectively.

In one systematic meta-analysis by Bristow et al., where 40 cohorts of 2019 patients with recurrent EOC were identified over a period of 24 years, it could be clearly shown that, after controlling of all other disease-related factors, each 10 % increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3-month increase in median cohort survival time (Bristow 2009).

Despite the very encouraging retrospective data, it is still not clear if the actual tumor resection is significantly influencing survival or if it is just a surrogate marker of more "favorable" tumor biology and therefore associated with a better overall prognosis. The first two prospectively randomized surgical trials will definitely answer this question, change clinical practice worldwide, and set new evidence-based standards.

12 Value of Tertiary Cytoreduction

The scenery is even more vague and undefined in the second relapse of EOC. Obtaining palliation in cases of severe tumor-induced symptoms like bowel obstruction may often be the main purpose of tertiary cytoreduction (TCS); still, the potential prolongation of survival and improvement of quality of life may also constitute relevant goals even in a tertiary setting of this chronic disease. Experiences regarding TCS were recently only limited in six monocentric analyses including a small number of patients. All conclude mainly to the fact that TCS may indeed offer a survival benefit in a highly select group of recurrent EOC patients and that this benefit appears to be greatest in those patients in whom a complete gross resection can be achieved (Shih et al. 2010; Hizli et al. 2012). Leitao et al. was the first to report on 26 patients who had undergone TCS at a single institution (Leito et al. 2004). Treatment-free interval before TCS and current postoperative residual disease could be identified as independent prognostic factors for survival, whereas time to first recurrence failed to retain prognostic significance in the multivariate analysis. Interestingly, platinum resistance failed to be identified as being significantly associated with a more dismal outcome. No independent factors predicting optimal cytoreduction could be identified among common clinical factors such as advanced age, residual disease after initial surgery, time to first recurrence, time from second cytoreduction, platinum-sensitivity as well as size and site of tumor-recurrence.

A further retrospective report by Karam et al. (2007) evaluating the outcome of 47 EOC patients undergoing tertiary cytoreduction confirmed the statistically significant superior overall survival in patients with microscopic versus macroscopic residual disease (24 vs. 16 months). After controlling these analyses for age, time to progression, and optimal residual disease during TCS, the authors identified only the presence of diffuse peritoneal carcinosis, at tertiary exploration as significant predictor of a worse overall survival. In a subanalysis of patients with limited disease implants, multivariate analysis could indeed indicate that total macroscopic tumor clearance at TCS retains prognostic significance of overall survival, so that the authors concluded that size of disease implants on preoperative imaging may guide the selection of ideal candidates for TCS. Regarding the assessment of potential preoperative predictors of optimal TCS, the authors could identify only tumor size (<5 cm) as a statistically significant predictor of complete tumor resection at TCS. Other variables like presence of ascites, initial disease-free interval, age at TCS, and limited number of disease sites on preoperative imaging (i.e., <4) could not show any significant impact.

In a smaller analysis including only 20 patients, the authors concluded to opposing results, challenging the benefit of TCS in EOC (Gultekin et al. 2008). Multivariate analysis could identify neither any significant predictors for optimal cytoreduction nor any significant prognostic factors for survival. Major intrinsic pitfalls of this particular analysis are though, as emphasized by the authors themselves, the small sample of patients, rendering a multivariate analysis to

have to be interpreted with caution. Furthermore, the authors defined as "optimal" cytoreduction residual disease of <2 cm, and not, as universally accepted, microscopic or <0.5 cm tumor residuals.

The largest monocentric TCS analysis evaluated 135 patients, and identified tumor involvement of the middle abdomen and peritoneal carcinomatosis as the two only parameters negatively affecting tumor resection (Fotopoulou et al. 2011).

A recent project published the largest multicentric analysis on TCS worldwide including 406 patients (median age, 55y; range,16–80) who underwent TCS between 1997 and 2011 in 12 centers across Europe, the USA, and Asia (Fotopoulou et al. Jan 2013). This represents the largest series so far in the tertiary setting of the disease and considering the fact that the conduction of any prospectively randomized trial in this advanced stage will be very challenging if not impossible, this constitutes currently the most valuable source of experience. The majority of the patients had an advanced initial FIGO stage III/IV (69 %), peritoneal carcinomatosis (51.7 %), and absence of ascites (72.2 %). Two hundred twenty-four (54.1 %) patients underwent complete tumor resection. The most frequent tumor dissemination site was the pelvis (73 %). This confirmed the knowledge from the previous results that even in the tertiary setting complete macroscopic tumor clearance plays a significant role both on overall and progression-free survival overruling the factor peritoneal carcinomatosis which failed to retain any prognostic significance on survival after controlling for tumor residual status. Median OS for patients without versus any tumor residuals was 49 versus 12 months. Most importantly, common clinicopathologic characteristics such as tumor stage, age, and histological subtype, which have been shown to be of significant predictive value at initial presentation of the disease, did not appear to be of any prognostic significance at the tertiary stage. A significant impact of third line postoperative systemic chemotherapy on overall survival was identified, emphasizing the importance of combinative systemic and surgical treatment in the fight against EOC even in this heavily pretreated patient collective. This may nevertheless constitute a selection bias since those patients who were fit enough and able to tolerate chemotherapy following radical surgery have theoretically also more favorable survival rates than patients too weak to tolerate any systemic treatment or even so advanced and multifocal metastasized that no chemotherapy was indicated. Rates of major operative morbidity and 30-day mortality were 25.9 % and 3.2 %, respectively, hence slightly higher than the equivalent data of secondary patients at the DESKTOP series; however here not only platinum-sensitive patients for cytoreduction were included but also palliative symptomatic patients who underwent surgery aiming at amelioration of symptoms. The most common complication was infection/sepsis by 13 %, a 4.4 % relaparotomy rate, but interestingly without any higher rates of thromboembolic events (2.5 %).

Multivariate analysis identified platinum-resistant, tumor residuals at secondary surgery and peritoneal carcinomatosis to be of predictive significance for complete tumor resection, while tumor residuals at secondary and tertiary surgery, decreasing interval to second relapse, ascites, upper abdominal tumor involvement, and non-platinum third-line chemotherapy, significantly affected OS.

Again here, like at secondary surgery, correct selection of surgical candidates is crucial to minimize morbidity and maximizing benefit from this radical approach in a highly palliative patient cohort.

13 Beyond Tertiary Cytoreduction: Quaternary Surgery

Venturing even beyond tertiary cytoreduction, the evidence is very scarce. There are only two series internationally to systematically evaluate the results of quaternary surgery in EOC. The largest series of 49 recurrent EOC patients demonstrated that even in a quaternary setting, nearly 33 % complete tumor resection rates are feasible in a highly specialized gynecologic oncologic center, despite the fact that the majority of the patients

had peritoneal carcinomatosis (77.6 %) (Fotopoulou et al. April 2013). According to prospectively documented intraoperative tumor mapping, patients presented with the following tumor pattern: lower abdomen 85.7 %, middle abdomen 79.6 %, and upper abdomen 42.9 %. Median duration of surgery was 292 min and hence equivalent to the duration of primary and secondary cytoreduction. Rates of major operative morbidity and 30-day mortality were 28.6 % and 2 %, respectively. Also noted were highly significant differences in survival between tumor-free and not tumor-free patients. Mean OS for patients without any tumor residuals was 43 months as opposed to only 13.4 months for patients with any residual disease. Mean OS for patients who received postoperative chemotherapy (n = 18; 36.7 %) was 40.5 months versus 12 months for those who did not, also highly a significant difference, corresponding so with the results of the TCS.

Multivariate analysis indentified multifocal tumor dissemination to be of predictive significance for incomplete tumor resection, higher operative morbidity, and more dismal survival. Interestingly, otherwise established prognostic factors such as ascites, platinum resistance, high-grade histology, and advanced age appeared not to carry any significant impact on survival.

The second monocentric analysis includes 15 patients and originates from the Memorial Sloan Kettering Cancer Center (Shih et al. 2009). Their findings showed comparable results: the number of sites of recurrence and optimal tumor debulking were associated with a prolonged survival, especially when a total macroscopic tumor clearance could be obtained. They also reported that all other well-established predictive factors for primary ovarian cancer and first relapse such as time to recurrence and response to platinum failed to retain any prognostic value on survival.

Still, especially in this advanced situation of the disease indication for cytoreduction, aiming at a putative amelioration of survival should be done only with high caution, careful patient selection, and clear discussion with the patients about the chronic and palliative situation of the disease and weighing of risks and benefits.

14 Salvage Surgery in Acute Situations: Bowel Obstruction and Intestinal Perforation in the Era of Targeted Antiangiogenetic Agents

EOC appears to behave differently from other epithelial cancer types, since its constant, almost pathognomonic feature is its local and lymphatic dissemination to the peritoneal and pleural layers by a paucity of visceral distant metastases via hematogenous pathways. Locoregional peritoneal disease is what most patients die from, in terms of bowel obstruction, cachexia, hypoproteinemia from ascites, organ failure, and exhaustion. Attributed to this diffuse tumor dissemination pattern along the peritoneal layers, EOC patients often present with the clinical picture of impaired intestinal passage or even bowel obstruction in the advanced primary and especially relapsed EOC. The newly emerging novel implementation of targeted therapies with antiangiogenetic potential may additionally favor fistula formation or intestinal perforation. EOC complicated by such severe and acute events constitutes a therapeutic dilemma. Massive systemic and surgical pretreatment and extensive tumor dissemination combined by acute systemic inflammatory immunologic response make any surgical intervention in this setting highly challenging, while associated with high morbidity and mortality rates (Sehouli et al. 2012). Appropriate balancing of risks and benefits is required to design the optimal treatment options tailored around the individual needs. The patient communication processes are currently based on rather scattered monocentric data series, since data from large multicenter analyses are broadly lacking. Surgical interventions include various surgical techniques and strategies, such as en bloc resections of the involved intestinal package and terminal proximal ileo- or jejunostomy, since due to the severe peritoneal carcinosis and inflammation, no plane dissection with anastomotic and repair techniques is feasible.

Short bowel syndrome with subsequent total parenteral nutrition (TPN) is therefore in some cases inevitable and requires high institutional and physical resources.

In cases of acute intestinal complications such as perforation and peritonitis, therapeutic approaches are rather limited. The cancer-induced tissue alterations and the overall low patient reserve constitute a major challenge for both the patients themselves and the treating physicians so that often such acute situations provoke a therapeutic nihilism and overall hesitation of active surgical measures. Retrospective analyses have shown that patients operated on in acute situations had significantly higher rates of anastomotic insufficiency compared to those operated within a planned setting, as also that the anastomotic insufficiency rate seems to be higher at primary debulking with tumor residuals compared to those without. For these reasons, even though no randomized trials exist to prove the safety or not of a primary anastomosis in an acute setting with peritonitis, the high probability of an intestinal stoma should be preoperatively discussed with the affected patients.

EOC rarely develops true visceral metastases; organ involvement is mainly due to direct extension by continuous tumor growth of the visceral peritoneum. Based on this, tumor resection is best achieved by an extraperitoneal approach of the tumor mass and en block dissection of all the tumor-involved organs together with the adjacent peritoneum, following their dissection from the ureteric and blood vessel level in the lower abdomen and duodenum, pancreas, and biliary duct in the upper abdomen. Extensive multivisceral techniques are increasingly therefore being included in the surgical armamentarium of advanced disease management (Fotopoulou et al. 2010). This reflects also the optimal approach in acute situations. A simple local intestinal resection with reanastomosis or barrel loop ileostomy is often not feasible, since the combination of peritoneal carcinosis and peritonitis makes a dissection in the physiological planes impossible and of high risk of further injury.

A major issue is also the highly crucial role of psychosocial and nutritional support network to provide TPN at home. Multidisciplinary teams consisting of nutritional specialists, dieticians, gastroenterologists, and psycho-oncologists are therefore indispensable for the successful outcome of such surgeries.

15 Systemic Treatment of Epithelial Ovarian Cancer

15.1 Early-Stage Disease (FIGO I-IIb)

Adjuvant platinum-based chemotherapy should be discussed and offered in all cases of early ovarian cancer apart from Ia/Ib G1 not only in case of incomplete staging but also to optimally staged higher-risk early disease, such as higher grade or serous subtype (WHO 2014).

Two prospectively randomized trials examined the value of chemotherapy after surgery in early-stage ovarian cancer. ACTION and ICON1 included a broad range of early-stage patients with grade 2 and 3 stages IA/B and all grades of stages IC/IIA, in order to recruit sufficient patients. The primary analysis of ICON1 on its own, with a median follow-up of 4-years demonstrated a significant improvement in both RFS and OS in favor of immediate adjuvant chemotherapy with six cycles of single agent carboplatin (AUC 5/6). Very similar findings were reported in the ACTION trial in which the majority of patients received a platinum-based combination chemotherapy.

A recent Cochrane meta-analysis of five large prospective clinical trials (four of ten with platinum-based chemotherapy) shows that chemotherapy is more beneficial than observation in patients with early-stage ovarian cancer. Patients who received platinum-based adjuvant chemotherapy had better OS and PFS than patients who did not receive adjuvant treatment. Nevertheless, in all abovementioned trials, only approximately one third of the patients were optimally staged, the remainder having a 30 % chance of being understaged and harboring occult disease. Despite this, benefit for chemotherapy in optimally staged patients cannot be excluded and adjuvant chemotherapy should be discussed and offered to all patients with high-risk early-stage ovarian cancer.

The addition of targeted therapies such as bevacizumab and other VEGF inhibitors such as nintedanib and cediranib, tyrosine kinase inhibitors, or PARP inhibitors is not of any established evidence, so far, and should not be offered outside clinical trials.

15.2 Advanced Stage Disease (FIGO IIc – IV)

Platinum-based chemotherapy ± paclitaxel is the, as per national and international guidelines dictated, first-line chemotherapy. The standard of care for most is thus carboplatin (AUC5/6) and paclitaxel (175 mg/m^2) given 3 weekly for six cycles. Dose-dense scheduling of the paclitaxel (80 mg/m^2 days 1, 8, 15 every 21 days with carboplatin AUC 5/6 on day 1) has been shown to improve overall survival in a large prospective randomized Japanese trial where Paclitaxel was applied in the dose of 80 mg/m^2. These findings have not been confirmed yet in the Caucasian population. A similar Italian study by the MITO group has shown a better tolerability of the weekly arm; however, it failed to demonstrate any survival benefit by a paclitaxel dose of 60 mg/m^2 and hence lower to the Japanese equivalent study. The just completed UK-based ICON 8 trial will in a few years answer the question of value of dose density in first-line chemotherapy for ovarian cancer and hence potentially establish standards of care.

For those patients who develop allergy to or do not tolerate paclitaxel, the combination of docetaxel-carboplatin or pegylated liposomal doxorubicin-carboplatin can be considered as an alternative regime based on two randomized clinical trials that showed similar efficacy.

Addition of bevacizumab concurrently to chemotherapy as maintenance for up to 12 months afterward in the ICON 7 and for 15 months in the GOG 218 has been shown to significantly prolong PFS and OS in patients with documented residual disease and/or distant metastases (grade A). The antiangiogenic VEGF inhibitor, bevacizumab, has been shown to improve overall survival when given together with carboplatin and paclitaxel 3 weekly as maintenance for up to 12 months total, in a higher-risk subgroup of these patients, who have been suboptimally debulked (1 cm residual disease) or had no surgery or stage IV disease (ICON 7). However, in the GOG 262 study, no survival benefit was seen in the bevacizumab arm if patients received paclitaxel in a weekly regime, even though there was no prior randomization to bevacizumab versus placebo. The value and safety of bevacizumab in the neoadjuvant setting is currently the objective of various ongoing randomized trials.

The value of intraperitoneal (IP) chemotherapy continues to be strongly controversial despite the efficacy that has been shown in different prospective randomized trials; an effect that seems to pertain even decades later. The lack of broad acceptance seems to be due to the reported high toxicity and high drop-off rates in the IP arm, but also due to the fact that it is not clear whether the survival benefit is due to the dose-dense application of iv paclitaxel or to the IP application per se. Currently ongoing trials with dose regimes equivalent to the intravenous version will answer the question of value of IP chemotherapy.

Despite the initial high response rates to first-line platinum-based therapies, the majority of patients with EOC will experience relapse and die of the disease. Several therapeutic options are available and the decision as to which therapy to commence is dependent on the platinum-free interval (PFI), even though in the last Ovarian Cancer Consensus Conference (OCCC) in Tokyo, the consensus was to rather abandon the traditional 6-month cutoff as outdated and rather define treatment-free interval (TFI) of TFIp (platinum), TFInp (non-platinum), and TFIb (biological agent to be specified). Traditionally the platinum-free interval has been considered as a predictor of response to future platinum-based treatment, even though now-emerging theories support approaches of "platinum resensitization" by extending the platinum-free interval with agents like trabectedin.

15.3 Intermediate Platinum Response (PFS 6–12 Months)

Patients with an intermediate response to platinum (i.e., PFI between 6 and 12 months) represent a therapeutic challenge. Various trials exist addressing only this special patient subset. The Italian study group MANGO leads the OVATYON trial evaluating PLD 30 mg/m^2 1 h i.v. + carboplatin AUC 5 30–60 min i.v. on day 1 q4 weeks; treatment was allowed to six cycles or progression versus PLD 30 mg/m^2 1 h i.v. + trabectedin 1.1 mg/m^2 3 h i.v. on day 1 q3weeks, up to six cycles or progression in EOC relapse patients with a PFI of 6–12 months.

A further study is the phase III MITO-8- (Efficacy Study of Chemotherapy to Treat Ovarian Cancer Recurrence and to Prolong the Platinum Free Interval). This study aims to test the hypothesis that the artificial prolongation of the platinum-free interval with a non-platinum treatment will improve the effectiveness of overall therapy in patients with EOC progression occurring 6–12 months after first-line treatment with a platinum derivative. The study groups MANGO and AO-Ovar are also participating, and a total number of 46 patients of the overall estimated 253 have already been recruited. In the experimental arm patients are treated with stealth liposomal doxorubicin followed at a later progression by carboplatin and paclitaxel, while in the conventional arm patients receive carboplatin and paclitaxel followed at a later progression by stealth liposomal doxorubicin.

15.4 Platinum Resistant/Refractory EOC Relapse (PFI $<$6 Months)

This is a difficult group in which to demonstrate benefit. Sharma et al. reported recently their experience of extended weekly carboplatin and paclitaxel in an attempt to increase response to chemotherapy in this special population. Twenty patients with platinum-resistant/refractory ovarian cancer received carboplatin AUC 3 and paclitaxel 70 mg/m^2 on day weekly. The RECIST response rate was 60 % by radiological criteria (RECIST) and 76 % by CA125 assessment, comparably very high for this platinum-resistant situation. Despite the dose-dense regimen in this heavily pretreated patient collective, no grade 3/4 thrombocytopenia occurred. The dynamics of response to dose-dense therapy were as rapid as with front-line therapy within the same patient. The authors state that this dose-dense regimen is routinely extended to at least 18 weekly cycles over 6 months and that it forms a highly active and tolerable cytotoxic scaffold to which molecular-targeted therapies can be added in platinum-resistant ovarian cancer.

Like in the primary also in the recurrent situation of the disease, targeted therapies are being implicated into conventional cytotoxic regimens to enhance response. Various antiangiogenics and small molecules such as sorafenib, bevacizumab, cediranib, zibotentan (ZD4054), and farletuzumab (MORAb-003) are being evaluated.

The multicenter AURELIA trial showed a significant prolongation of PFS in platinum-resistant patients who were treated with bevacizumab additionally to non-platinum monotherapy (liposomal pegylated doxorubicin or paclitaxel weekly or topotecan); however equivalent to the platinum-sensitive trials, bevacizumab failed to show any significant effect on overall survival.

16 Follow-Up

The aim of follow-up is not only to detect relapse and direct patients toward future therapeutic approaches but also to help the patients cope with the chronic effects of the anticancer treatment they had such as polyneuropathy, gastrointestinal symptoms, etc.

Duration of follow-up and intervals between follow-up visits vary according to local practices, but generally every 3 months for the first years and then every 6 months, even though there is no randomized trial to prove survival benefit of strict follow-up protocols versus an individualized

patient and symptom-led approach. Rises in CA125 can be used to document progressive disease in patients who achieve a normal CA125 after primary treatment but tend to precede symptomatic relapse by a median of 4.5 months (range 0.5–29.5 months). A recent MRC/EORTC trial demonstrated no difference in overall survival between patients who received chemotherapy based on a rising CA125 and those who did not receive chemotherapy until they were symptomatic. Although the value of routine CA125 measurements was negated by this randomized controlled trial (RCT), some patients prefer to know as accurately as possible what might lie ahead and can cope with the knowledge that a rising CA125 indicates that their cancer has returned and yet immediate treatment is not necessarily of any benefit.

Participation in first-line trials also generally requires regular CA125 measurements in order to accurately determine trial end points. But rising CA125 alone without clinical or radiographic evidence of recurrence is not sufficient enough to commence systemic chemotherapy.

The results of the upcoming prospectively randomized DESKTOP III and GOG 0213 will nevertheless newly define and potentially change follow-up practice if tumor-free secondary debulking will be shown to be associated with survival benefit, in which case tumor burden at the time of secondary surgery will impact on surgical complexity, morbidity, and overall outcome. Furthermore, in the increasingly emerging era of targeted agents and maintenance approaches, additional monitoring with CA125 may identify patients with early relapse (i.e., within 6 months) who may be suitable for phase 2 clinical trials with investigational new agents.

At follow-up visits, a careful history is imperative, together with clinical examination. CA125 measurement is not mandatory and has not been proven to be of prospective survival benefit. All patients should have the contact details of their key worker so that they can have early local review for unexpected symptoms.

17 Conclusion

To conclude, epithelial ovarian cancer is a complex disease which is difficult to detect in its early stages due to its vague symptom pattern and has a high mortality rate owing to the aggressive nature of the majority of tumors. No effective screening protocol has been designed as yet and so it continues to present at advanced stages. Work is ongoing, especially in proteomics, to discover a marker which can be used to detect cancer and then guide follow-up; however finding a universal marker is difficult due to the broad inter-tumor heterogeneity demonstrated by these cancers.

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Diagnosis and Management of the Cancer of the Uterus

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Abstract

Uterine cancer is the most common malignancy of the female genital tract. Treatment of uterine cancer is related to cell type, grade, and stage. However, the vast majority of uterine cancers will be low grade, early stage endometrial cancers with obesity being the primary risk factor associated with these cancers. Surgery is an important part of staging and management of uterine cancers.

Keywords

Uterine cancer • HNPCC • Lynch syndrome • Endometrial cancer • Sarcoma • Staging endometrial stromal cancer

1 Introduction

As the most common gynecologic cancer seen in North America and Europe, uterine cancer can be encountered by anyone who provides healthcare to women. While the majority of these cancers will be cured with treatment, management can be controversial and confusing. This chapter will discuss the epidemiology, pathology, genetics, and treatment of this common malignancy.

2 Epidemiology

Uterine cancer is the 6th most common cancer in women worldwide, with over 218,100 new cases diagnosed each year. In North America and Europe, endometrial cancer is the most common malignancy of the female reproductive tract, the 4th overall most common cancer diagnosed in women, and the 8th most likely cause of cancer death (Jemal et al. 2011). It is estimated that 49,560 US women will be diagnosed with uterine cancer in 2013 (age-adjusted incidence rate 24.5/100,000) and 8,190 will die of their disease (SEER 2013).

Ninety-five percent of cancers of the uterine corpus arise from the epithelial cells of the endometrium. Endometrial cancer is more common in postmenopausal women, with the mean age of diagnosis of 60 and the majority of patients being over the age of 50 (Sorosky 2012). The greatest risk factor for endometrial cancer is hyperestrogenic states including estrogen producing tumors, unopposed exogenous estrogen, and increased adiposity. Early menarche, late menopause, and nulliparity also increase exposure to estrogen and are associated with an increased risk of uterine cancer.

Among obesity-related cancers in women, endometrial cancer is most strongly associated with increasing body mass, with 49 % of cases in the US attributable to obesity (Renehan et al. 2008). Regional and racial differences in rates of endometrial cancer are additionally linked to rates of obesity and hormone use. Conversely, factors that reduce estrogen levels such as smoking, physical activity, oral contraceptive usage, and multiparity are protective against endometrial cancer.

Uterine sarcomas originate from the muscle and connective tissue of the myometrium. They comprise 2–5 % of uterine cancers and less than 1 % of all gynecologic malignancies. In the USA, approximately 1,500 uterine sarcomas were diagnosed in 2013. Risk factors include a history of pelvic irradiation and black race. The peak incidence differs for the type of sarcoma. Leiomyosarcomas affect women at a mean age of 53, with many being premenopausal at diagnosis (SEER 2013; Pautier et al. 2014).

3 Genetics

The majority of uterine cancers are sporadic with approximately 1 in 10 associated with a genetic syndrome. Hereditary nonpolyposis colon cancer (HNPCC) syndrome is the most common genetic syndrome associated with endometrial cancer. The NCCN recommends genetic counseling should be considered in women diagnosed under the age of 55, and those who have a family history of colon cancer and endometrial cancer. HNPCC, also known as Lynch Syndrome, is associated with microsatellite instability in the mismatch repair genes MLH1, MSH2, MSH6, PMS2, or EPCAM, predisposing to cancers arising from

the endometrium, colon, ovary, upper gastrointestinal tract, genitourinary tract, and other sites (ACOG 2014).

Approximately 50 % of women with Lynch syndrome will present with endometrial cancer. Women with Lynch syndrome should be offered a risk reducing hysterectomy and bilateral salpingo-oophorectomy after child bearing is complete. For women who wish to maintain their fertility, there is no clear evidence that screening for uterine cancer is effective but annual pelvic ultrasound and/or endometrial sampling is common practice (ACOG 2014). The National Comprehensive Cancer Network (NCCN) states that annual endometrial biopsies are an option for cancer screening (NCCN 2012). The American College of Obstetricians and Gynecologists (ACOG) recommends endometrial sampling every 1–2 years starting at age 30–35 (ACOG 2014). Risk reduction via progestin-based contraception should also be considered in women that do not desire surgery. Surveillance for other cancers should be encouraged in these patients and genetic counseling should be considered for themselves and family members (Sorosky 2012; Lynch syndrome 2014).

Cowden Syndrome is associated with multiple hamartomas and increased risk of cancers including endometrial, breast, and thyroid. The most common mutation in Cowden Syndrome is PTEN, but mutations in SDHB, SDHD, and KLLN have also been seen. There is no evidence to support risk reducing hysterectomy, but this should be discussed with women with this syndrome (Cowden syndrome 2014).

Women with a history of retinoblastoma are at an increased risk for leiomyosarcoma. Retinoblastoma is associated with inactivation of the RB1 tumor suppressor gene. When the gene mutation involves all cells, there is increased risk for pinealoma, osteosarcoma, melanoma, and other muscle tumors (Retinoblastoma 2014).

4 Histology

Based on clinicopathological characteristics, Bokhman devised a dualistic classification of endometrial cancers. Type 1 lesions are the most common, comprising 80 % of endometrial cancers. They include endometrioid cell type or variants (such as squamous differentiation, villoglandular, and secretory), are usually well to moderately differentiated, and are less likely to metastasize outside of the uterus. These tumors often occur in women with a history of anovulatory uterine bleeding and can be found in a background of endometrial hyperplasia. Women with a biopsy of complex endometrial hyperplasia with atypia have a 40 % likelihood of having malignancy found in the hysterectomy specimen (Trimble et al. 2006).

Type II lesions include clear cell carcinoma, serous adenocarcinoma, and carcinosarcoma and are not associated with hyperestrogenism. These malignancies are poorly differentiated and more aggressive; deep myometrial invasion and metastic disease are more common than with type I tumors. Recurrence is more likely and survival is worse for type II uterine cancers. Serous carcinoma is characterized by papillae and has highly pleiomorphic tumor cells with necrosis and many mitoses. Endometrial intraepithelial carcinoma (EIC) is a rare finding, but it is thought to be the precursor lesion in serous tumors of the uterus. It involves pleiomorphic but noninvasive tumor cells (Trimble et al. 2012). Carcinosarcoma, also known as malignant mixed mullerian tumors, contain mixed components of sarcoma and adenocarcinoma. While it historically had been grouped with sarcomas, more recent evaluation has suggested that it is more similar to a dedifferentiated carcinoma than a sarcoma. Staging of carcinosarcoma is now included in the FIGO staging of endometrial carcinomas (Mutch 2009).

Uterine sarcomas include leiomyosarcomas, mixed epithelial and stromal tumors (carcinosarcoma and adenosarcoma), and endometrial stromal sarcomas. Leiomyosarcomas make up 30 % of all uterine sarcomas. Sarcomas arising in the endometrial stroma account for 15 % of all uterine sarcomas. Other sarcomas include mixed endometrial stromal and smooth muscle tumors, adenosarcomas, embryonal botryoides or rhabdomyosarcomas, and perivascular epithelial-cell tumors (PEComas) (D'Angelo and Prat 2009).

Table 1 2009 FIGO staging of endometrial carcinoma (Mutch 2009)

Stage 1	Tumor confined to the corpus uterus
1a	No or less than ½ myometrial invasion
1b	Invasion ≥ half of the myometrium
Stage 2	Tumor invades cervical stroma
Stage 3	Local and/or regional spread of tumor
3a	Tumor invades serosa of the uterus and/or adnexae
3b	Vaginal and/or parametrial involvement
3c	Metastases to pelvic and/or paraaortic lymph nodes C1: positive pelvic nodes C2: positive paraaortic nodes with/without positive pelvic nodes
4	Tumor invades bladder and/or bowel mucosa and/or distant metastases
4a	Tumor invasion of bladder and/or bowel mucosa
4b	Distant metastases including intra-abdominal metastases and/or inguinal lymph nodes

5 Diagnosis/Screening

Clinical features associated with uterine cancer include abnormal uterine bleeding, abnormal cervical cytology (e.g., atypical glandular cells on a cervical cytology), pelvic pain, and an enlarging pelvic mass. Approximately 90 % of women with endometrial cancer present with abnormal bleeding. The diagnosis is obtained by pathological review of tissue, preferably obtained by endometrial biopsy, dilation and curettage, or hysteroscopy and biopsy. While these methods are very efficacious for detecting uterine cancers, if the lesion does not invade into the endometrial cavity, leiomyosarcoma may only be diagnosed after hysterectomy or myomectomy. Screening asymptomatic women for uterine cancer is not recommended (NCCN 2012).

6 Staging

The NCCN recommends a history and physical examination, chest x-ray, endometrial sampling, and cervical cytology for the initial workup for uterine cancer. Traditionally, staging of endometrial cancer involves an exploratory laparotomy, total abdominal hysterectomy, bilateral oophorectomy, and pelvic and paraaortic lymph node dissections (NCCN 2012).

Grade 1 tumors are well differentiated, with formed glands and no more than 5 % of non-squamous solid components. Grade 2 contains 6–50 % solid components and grade 3 has greater than 50 % non-squamous solid components. If there is significant cytologic atypia, the tumor should be upgraded. Currently, nearly 70 % of patients are diagnosed and treated at early stage with 5-year survival estimated at 95.8 %, and an additional 20 % are diagnosed with only regional disease with a 5-year survival estimated at 67.0 % (SEER 2013) (Tables 1 and 2).

7 Management of Endometrial Cancer

Unless prohibited by patient comorbidities, surgery is usually the first step in the management of endometrial cancer. Comprehensive surgical staging traditionally includes a hysterectomy, bilateral salpingo-oophorectomy, lymph node assessment, and intraperitoneal cytology. However, much of the traditional recommendations for surgical management of endometrial cancer have been challenged recently.

While hysterectomy is indicated for women with endometrial cancer, the best surgical approach has been questioned. There have been multiple studies demonstrating the safety and efficacy of laparoscopic surgery for endometrial cancer staging. Proven benefits include improved quality of life, shorter hospital stay, and less blood loss than exploratory laparotomy. In addition, laparoscopy does not impact recurrence rates or survival (Zullo et al. 2012; Walker et al. 2012). Since the introduction of the DaVinci robotic surgical platform, its use has continued to climb. The literature demonstrating the safety and efficacy of robotic staging is growing. A clear benefit of utilizing the robot is the ability to stage obese patients minimally invasively (Seamon et al. 2009).

Table 2 2009 FIGO staging of uterine sarcoma (Mutch 2009)

Stage 1	Tumor confined to the corpus uterus
1a	Less than 5 cm
1b	≥5 cm
Stage 2	Tumor extends to the pelvis
2a	Adnexal involvement
2b	Tumor extends to extrauterine pelvic tissue
Stage 3	Tumor invades abdominal tissue
3a	One site
3b	More than one site
3c	Metastasis to pelvic and/or paraaortic lymph nodes
4	Tumor invades bladder and/or rectum and/or distant metastases
4a	Tumor invasion of bladder and/or rectum
4b	Distant metastases
*Endometrial stromal sarcoma	Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors
*Adenosarcoma Stage 1	1a: tumor limited to endometrium/endocervix (without myometrial invasion) 1b: tumor invades ≤ ½ of myometrium 1c: tumor invades > ½ of myometrium

7.1 Lymphadenectomy

There continues to be significant debate regarding what population is at risk for nodal disease and warrants a lymphadenectomy. There is considerable variability in practice patterns amongst gynecologic oncologist with respect to indications for staging and extent of dissection. While lymphadenectomy guides staging and treatment, trials have failed to demonstrate either an overall survival or recurrence free survival benefit for pelvic lymphadenectomy (Mariani et al. 2000).

7.2 BSO

Several studies have retrospectively evaluated the outcomes of premenopausal women with ovarian preservation during surgery for endometrial cancer without finding any adverse survival impact. Given the impact on quality of life and increase in cardiovascular risk factors, it may be reasonable to forgo oophorectomy in premenopausal women with early-stage low-risk endometrial cancer (Lau et al. 2014; Lee et al. 2013; Wright et al. 2009). This should be carefully considered by the patient and her gynecologic oncologist. The benefit of retaining the ovaries in a postmenopausal woman has not been evaluated and bilateral salpingo-oophorectomy is recommended.

7.3 Cytologic Assessment

Pelvic washings were included in surgical staging for endometrial cancer prior to the 2009 FIGO staging. The findings of positive cytology are not correlated with clinical outcomes, and their utility has been questioned. As of the 2009 FIGO staging, pelvic washings are no longer required as part of surgical staging for endometrial cancer, and many gynecologic oncologists no longer include intraperitoneal cytology as part of their staging surgery (NCCN 2012).

8 Risk Assessment

Surgical stage and other significant pathologic risk factors are utilized to determine patients' risk for persistent disease or recurrence. This risk assessment is often utilized to determine the need for adjuvant therapy. Risk assessment and determination of adjuvant therapy can be complex and should be managed by an oncologist experienced in the treatment of uterine cancer.

8.1 Low Risk

Patients at low risk of recurrence have endometrioid histology with disease confined to the endometrium. This includes a subset of patients with stage IA and grade 1 or 2 endometrial cancer. Typically these patients are managed with close surveillance alone following surgery (NCCN 2012).

8.2 Intermediate Risk

Patients with an intermediate risk for recurrence have disease confined to the uterus, including the cervix (stage II) with myometrial invasion (stage IA or IB). Other prognostic factors such as deep myometrial invasion, grade 2 or 3 histology, and the presence of lymphovascular invasion can further subdivide this group into low or high intermediate risk. Recurrence rates range from 5 % to 30 % with or without radiation therapy. As such, consideration for adjuvant radiation therapy is warranted (NCCN 2012; Keys et al. 2004; Creutzberg et al. 2000) (Table 3).

Patients with a high risk for disease recurrence have advanced stage disease, and grade 3 carcinomas (including serous and clear cell) of any stage. This category is associated with a high rate of recurrence and death from endometrial cancer. As such, adjuvant chemotherapy is often utilized postoperatively (NCCN 2012).

Table 3 Risk assessment of local stage endometrial cancer (high intermediate risk (HIR)group determination)

Study	Risk factor	Determination of HIR
Gynecologic Oncology Group	Deep myometrial invasion Grade 2 or 3 Lymphovascular space invasion	Any age with all 3 50–69 with 2/3 70 or older with 1/3
PORTEC	Deep myometrial invasion Grade 3	Age > 60 with both risk factors

8.3 High Risk

Currently there is not a "standard" approach for high-risk disease. Often adjuvant therapy is dictated by surgical and pathologic factors such as uterine or extra uterine disease. Since multiple questions remain, enrollment on a clinical trial may be the most appropriate option for patients in this risk category.

In advanced stage disease, chemotherapy with carboplatin and paclitaxel is the most use regimen. Other active agents include doxorubicin, ifosfamide, topotecan, oxaliplatin, docetaxel, ixabepilone, and pegylated liposomal doxorubicin (NCCN 2012). The role of combined chemotherapy and radiation therapy has not been defined in advanced disease.

8.4 Recurrent or Metastatic Disease

Chemotherapeutic options for recurrent or metastatic disease are the same as for advanced disease. In localized recurrence in patients without prior radiation, radiation therapy can be utilized. For patients in whom radiation or cytotoxic therapy is not a reasonable option, hormonal therapy is an acceptable alternative for therapy in recurrent disease. In tumors that express estrogen and progesterone receptors, a favorable response to endocrine therapy is likely (Decruze and Green 2007). Tamoxifen is currently the only selective estrogen receptor modulator to demonstrate activity (Thigpen et al. 2001). Aromatase inhibitors are currently under investigation.

9 Non-Endometrioid Histologies

9.1 Uterine Papillary Serous Carcinoma (UPSC)

UPSC represents a histologically aggressive subtype of endometrial carcinoma that typically presents with extrauterine disease with a spread pattern similar to papillary serous ovarian cancer. Although this histology accounts for 10 % of all endometrial cancers, it accounts for the majority of recurrences. Comprehensive staging for early stage UPSC is recommended in *all* patients. Multiple studies have clearly demonstrated that optimal resection of metastatic disease confers a survival benefit and should be the goal at the time of primary surgery. Any myometrial invasion is associated with higher risk of recurrence. Controversy also persists regarding the benefit of adjuvant therapy for disease confined to a polyp. Although the risk of recurrence is low in this population, it is not negligible (Rauh-Hain et al. 2010). Due to the propensity for uterine serous cancer to recur distantly, chemotherapy

has been considered as an essential component of adjuvant therapy (Fader et al. 2009).

For advanced stage disease, following optimal cytoreduction, chemotherapy is the recommended adjuvant therapy due to high risk of distant recurrence. Currently, the combination of paclitaxel and carboplatin is an appropriate choice of cytotoxic therapy for advanced stage UPSC. The role of radiation therapy is limited and not typically recommended (NCCN 2012).

9.2 Uterine Carcinosarcoma

As with endometrial carcinoma, surgery is the primary management for carcinosarcoma. Surgical staging is recommended. For advanced stage disease confined to the abdomen, cytoreduction is also recommended (Tanner et al. 2011). For stage I and II uterine carcinosarcoma, there is a relative paucity of quality data to recommend adjuvant therapy. In the limited number of trials that do exist, there is a consistent improvement in progression free survival but not overall survival (Cantrell et al. 2012). Chemotherapy was associated with improved progression free survival compared to observation or radiation therapy (Omura et al. 1985). The role for radiation therapy or chemotherapy is questionable for early stage disease. Given the paucity of data, consideration should be given to enrollment on a clinical trial. For stage III and IV uterine carcinosarcoma, chemotherapy is recommended as adjuvant therapy. Ifosfamide, cisplatin, adriamycin, and paclitaxel have had the most significant evidence of activity (NCCN 2012).

10 Sarcomas

10.1 Leiomyosarcoma

Uterine leiomyosarcoma is often identified incidentally following a hysterectomy or myomectomy for presumed uterine leiomyomas. The standard surgical management for women with known leiomyosarcoma is a hysterectomy often coupled with a bilateral salpingo-oophorectomy (BSO) in postmenopausal women. The role of a BSO has been questioned due to a growing body of literature failing to demonstrate a survival benefit. For those with disease outside of the uterus, the role of cytoreduction is controversial and not clearly understood. The role of a lymphadenectomy is also uncertain. Any bulky nodes should be removed. Standard staging when disease is confined to the uterus is questionable since the risk of nodal metastasis is low (Kapp et al. 2008; Major et al. 1993). In patients with an incidental finding of leiomyosarcoma on final pathology, a return to the operating room for "staging" is not indicated. Imaging to identify extrauterine disease is recommended.

The role of chemotherapy, radiation therapy, or a combination of the two is undetermined. Adjuvant therapy for early stage disease is especially controversial. As such, enrollment on a clinical trial should be recommended. The NCCN recommends observation versus consideration for chemotherapy, with docetaxel and gemcitabine being the preferred regimen. Other suggested regimens are listed in the Uterine Cancer guidelines (NCCN 2012).

With respect to recurrent disease, leiomyosarcoma commonly recurs in the lungs, liver, abdomen, pelvis, and retroperitoneal lymph nodes. Local recurrences in patients with a prolonged progression free survival can be managed with surgical intervention. For patients with a local recurrence who are not ideal surgical candidates, radiation therapy can be considered. Chemotherapy is the recommended approach for women with recurrent metastatic disease. The combination of gemcitabine and docetaxel is supported by multiple clinical trials. In the setting of recurrent disease, the chemotherapeutic agent of choice is often dictated by performance status, medical history, and patient choice. In the setting of recurrent metastatic disease, palliation is the goal of chemotherapy (NCCN 2012).

10.2 Adenosarcoma

Treatment for adenosarcoma of the uterus is hysterectomy with bilateral salpingo-oophorectomy

in postmenopausal women. As ovarian metastasis is uncommon, the ovaries can be left in premenopausal women. Lymphadenectomy is not required in disease confined to the uterus. As most adenosarcomas contain an endometrial stromal sarcoma component, adjuvant therapy should follow the ESS guidelines (Friedlander et al. 2014).

10.3 Endometrial Stromal Sarcoma

Hysterectomy is the primary treatment for early endometrial stromal sarcoma. Ovarian conservation may be considered in young women with small tumors. The role of lymphadenectomy is not well defined in this disease. In recurrent or advanced disease, cytoreductive surgery should be considered. As the rate of hormone receptor positivity is very high in endometrial stromal sarcoma, hormone therapy is recommended in advanced or recurrent low-grade disease. In high-grade disease, cytotoxic chemotherapy should be considered (NCCN 2012). Radiation therapy is often used for palliation as adjuvant pelvic radiation has not been shown to improve survival (Amant et al. 2014).

11 Conclusion

Uterine cancer is the most common gynecologic malignancy with a rising incidence in the United States. Endometrial cancers are associated with obesity and genetic syndromes such as HNPCC. They are histologically divided into type I and type II malignancies, with type I cancers usually being early stage and often curable. Type II cancers tend to be more aggressive and more often diagnosed at later stages of disease. Cancers of the uterine body include sarcomas such as leiomyosarcoma, adenosarcoma, and endometrial stromal sarcoma.

Abnormal uterine bleeding is the most common presenting symptom and should be evaluated with an endometrial biopsy. Following a diagnosis of uterine cancer, surgical staging is often performed. There are still many controversies regarding the need for a lymphadenectomy, and it is uncertain which patients need a complete lymph node dissection for prognostic information and guidance of therapy. Laparoscopic, robotic, and open approaches to staging are considered equivalent for cancer therapy and only differ in their operative risks.

The need for adjuvant therapy is determined by pathologic risk factors for recurrence. Patients at low risk for disease recurrence need no treatment after surgery. Those with an intermediate risk may benefit from chemotherapy and/or radiation. Patients with a high risk of recurrence need chemotherapy and radiation. All patients with a history of uterine cancer will need surveillance for recurrence of disease with frequent exams and biopsy of any suspicious lesion. Treatment of recurrent disease depends on the timing and location of recurrence.

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Endometrial Hyperplasia

Kristina Williams and Emily Ko

Contents

Abstract

Endometrial hyperplasia (EH), a known precursor to endometrial adenocarcinoma, is a common gynecologic diagnosis among women, typically resulting from an increase in endogenous or exogenous unopposed estrogen. EH is a histologic diagnosis that is characterized by one of the two classification schemas: either the widely used WHO94 criteria or the more standardized endometrial intraepithelial neoplasia (EIN) criteria. The risk of progression to cancer varies and depends on the severity of the lesion. Lesions with atypia have the highest risk of progression to cancer and the diagnosis of concurrent endometrial cancer. EH mainly effects perimenopausal or postmenopausal women. Significant risk factors for EH include obesity, chronic anovulation as seen in disorders such as PCOS, estrogen only hormone replacement, tamoxifen use, and Lynch syndrome. Clinical manifestations include abnormal uterine bleeding, postmenopausal bleeding, or atypical endometrial glands on pap smear, which require a diagnostic workup in peri-/postmenopausal women. Transvaginal ultrasound (TVUS) is typically the first diagnostic study to be performed in a woman with abnormal uterine bleeding (AUB). Either office endometrial biopsy (EMB) or dilation and curettage (D&C) with or without hysteroscopy can be performed to diagnose EH. When EH is diagnosed, management includes surveillance,

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hormone therapy, or hysterectomy and choice of therapy depends on the type of EH, potential risk for endometrial cancer, and patient characteristics (i.e., desire to maintain fertility and surgical candidacy). There are no current recommendations for screening for endometrial hyperplasia in the general population.

Keywords
Endometrial hyperplasia • Endometrial intraepithelial neoplasia • Abnormal uterine bleeding • Postmenopausal bleeding • Unopposed estrogen • Endometrial cancer

1 Introduction

Endometrial hyperplasia is a common condition defined histologically as an abnormal overgrowth of endometrial glands contained within the uterus. Clinically, it is important to recognize this condition as a precursor and marker for endometrial adenocarcinoma, the most common gynecologic cancer among American women (ACOG 2015; Armstrong et al. 2012; Trimble et al. 2012).

Normal endometrium changes throughout the menstrual cycle in response to estrogen and progesterone. Estrogen causes the endometrial lining to thicken by proliferation. After ovulation, the corpus luteum produces progesterone. If pregnancy is to occur, progesterone stabilizes the endometrium by inhibiting proliferation and stimulating differentiation. If pregnancy does not occur, progesterone production decreases and allows for shedding of the endometrial lining (Trimble et al. 2012).

Typically, in endometrial hyperplasia, unopposed estrogen (i.e., a lack of progesterone) causes the endometrial glands to proliferate such that there is an increase in gland to stroma ratio. Thus, endometrial hyperplasia affects those women that have intermittent or absence of ovulation (i.e., PCOS) or those women that have higher levels of circulating estrogens postmenopausally (i.e., HRT, obesity). The most common clinical manifestation of hyperplasia is abnormal uterine bleeding, which always requires diagnostic evaluation in a perimenopausal or postmenopausal woman. The mainstay of management of hyperplasia is the detection or prevention of endometrial cancer. This chapter will discuss the classification, epidemiology and risk factors, diagnosis, and management of endometrial hyperplasia.

2 Histology and Classification

The classification of endometrial hyperplasia is based on histology. There are currently two diagnostic classification systems used to categorize endometrial hyperplasia; the World Health Organization 1994 classification schema and the Endometrial Intraepithelial Neoplasia (EIN) diagnostic schema (Table 1).

2.1 WHO Classification

The WHO classification system divides endometrial hyperplasia into four subcategories based on glandular complexity and nuclear atypia (Fig. 1). The four subcategories include: (1) simple hyperplasia, (2) complex hyperplasia, (3) simple hyperplasia with atypia, and (4) complex hyperplasia with atypia. Simple hyperplasia is defined histologically as an overall increase in the number of endometrial glands with mild crowding. Frequently the glands exhibit dilation. Complex hyperplasia consists of a greater than 50 % gland to stromal ratio ("crowding"), which is a much higher ratio than that seen for simple hyperplasia. Additionally, the glands typically appear disorganized with mitoses present. In either simple or complex hyperplasia, the glandular cells may also show features of nuclear atypia. Nuclear atypia refers to the presence of nuclear enlargement, prominent nucleoli, or rounded nuclei (normally elongated) with either evenly or irregularly dispersed chromatin.

The widespread use of this classification schema is based on retrospective data showing correlation of risk of endometrial cancer with the presence or absence of nuclear atypia. The risk of

Table 1 Classification systems used for defining precancerous endometrial lesions

World Health Organization 1994 (WHO 94) classification system			
Class	Risk of progression (%)	Treatment	
Simple	1	Hormone therapy	
Complex	3	Hormone therapy or surgical treatment	
Simple with atypia	8	Surgical treatment or hormone therapy[a]	
Complex with atypia	29	Surgical treatment or hormone therapy[a]	
Endometrial intraepithelial neoplasia (EIN) classification system			
Class	Diagnostic criteria	Risk of malignancy	Treatment
Benign hyperplasia	Exclusion of EIN or cancer	0.60 %	Hormone therapy or surveillance
Endometrial intraepithelial neoplasia	Topographically diffuse	19 %	Hormone therapy or surgery
	Gland area > stromal area		
	Cells of lesion are cytologically different from background		
	Max linear dimension > 1 mm		
	Exclusion of carcinoma and "benign mimics"		
Endometrial cancer	N/A	N/A	Surgery

[a]Hormone therapy in these cases is reserved for women who desire to preserve fertility or for women who are poor surgical candidates or decline surgical treatment after being appropriately counseled References: (Armstrong et al. 2012; Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015; Trimble et al. 2012)

progression to endometrial cancer in a woman with simple hyperplasia is exceedingly low (1 %), while the risk of progression in a woman with complex atypical hyperplasia is as high as 29 %, requiring invasive treatments (Table 1; Kurman et al. 1985; Lacey et al. 2010). In this sense, the WHO classification system correlates well with risk of progression and is currently the most commonly used schema by pathologists.

Although this classification system has been in use for many years, it has never been subjected to rigorous verification, putting into question the validity of this schema. Furthermore, two of the subcategories of classification are relatively rare in the population, simple EH with atypia and complex EH without atypia. Simple EH is thought to be a benign lesion resulting from estrogen effect, whereas atypical EH is thought to be a precancerous lesion resulting from the combination of estrogen effect and genetic effects; thus some experts question the biologic significance of simple hyperplasia as it is overall benign and may frequently spontaneously resolve. Additionally, some experts have questioned the WHO classification given that each of the subclasses fails to be tied to a specific or different treatment option. Rather, largely the same treatments have been offered across EH subtypes.

The largest limitation of the WHO classification system is that there are no specific criteria for histologic diagnosis and thus interpretation is subjective and leads to high interobserver variability, especially when diagnosing cellular atypia. In a large prospective multicenter cohort study of complex EH with atypia, unanimous agreement of a diagnosis among three pathologists was observed in less than half of all diagnoses, and pathologists agreed with the initial diagnosis in only 38 % of cases (Zaino et al. 2006). For this reason, many have recommended the use of the EIN classification system rather than the WHO system, although this has not been universally adopted.

2.2 EIN System

The EIN classification system, developed and introduced by the International Endometrial Collaborative Group, uses three subcategories to

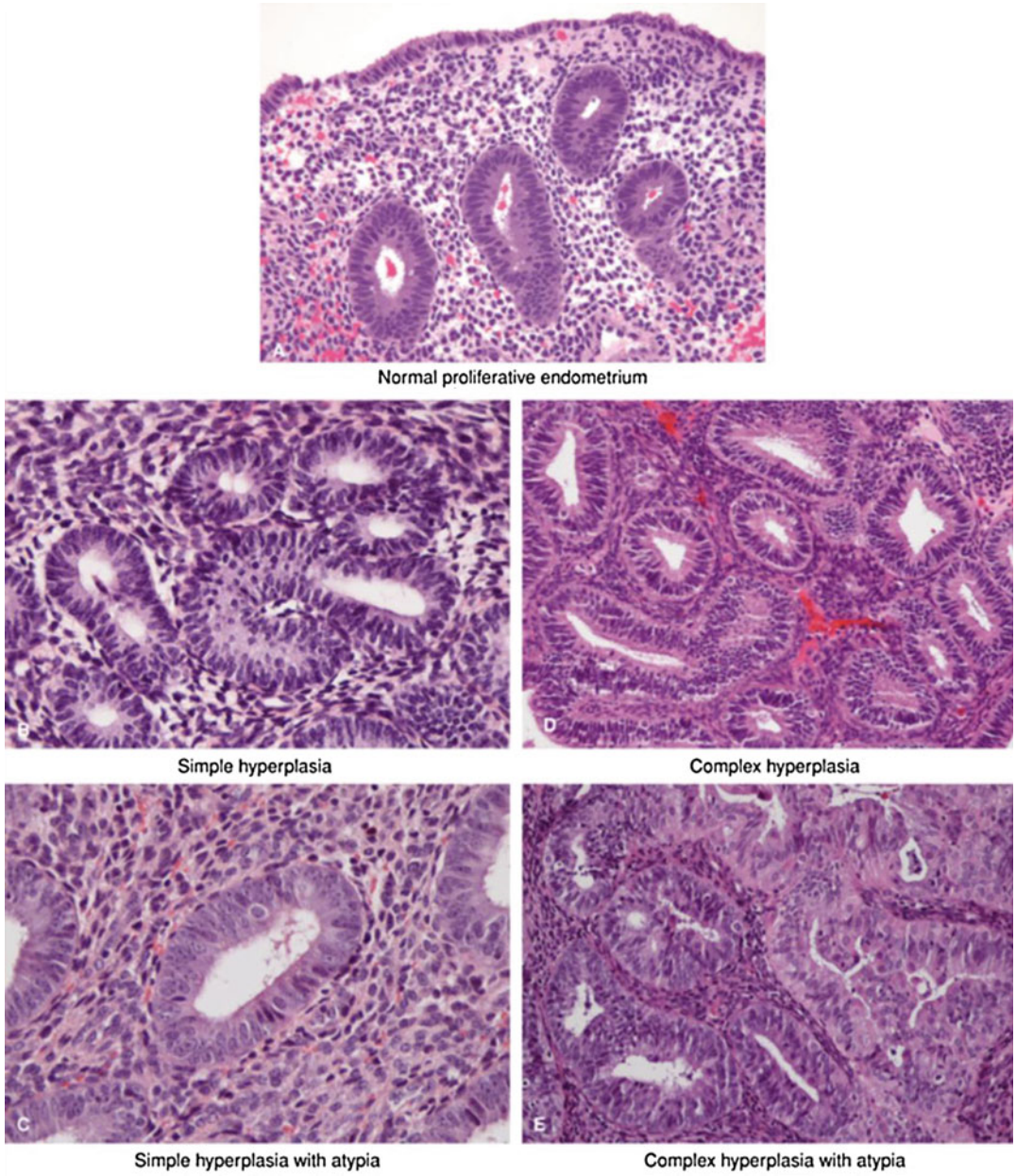

Fig. 1 Histology of endometrial hyperplasia (Originally published in Hoffman BL, Schorge JO, Schaffer JI, Halvorson LM, Bradshaw KD, Cunningham FG*: Williams Gynecology* , 2nd Edition' with kind permission of The McGraw-Hill Companies, Inc. All rights reserved. Photomicrographs display normal proliferative endometrium contrasted with different types of hyperplastic endometrium. (**a**). This high-power view of normal proliferative endometrium shows regularly spaced glands composed of stratified columnar epithelium with bland, slightly elongate nuclei and mitotic activity. (**b**). In simple hyperplasia, glands are modestly crowded and typically display normal tubular shape or mild gland-shape abnormalities. Nuclei are bland. (**c**). In this case, glands are only mildly crowded, but occasional glands, such as the one pictured in this high-power view, have nuclear atypia characterized by nuclear rounding and visible nucleoli. Cytologic atypia accompanies complex hyperplasia more often than it does simple hyperplasia. (**d**). In complex hyperplasia, glands are more markedly crowded and sometimes show architectural abnormalities such as papillary infoldings. In this case, gland profiles are fairly regular but the glands are markedly crowded. (**e**). Glands are markedly crowded and some show papillary infoldings. Nuclei show variable nuclear atypia. Some of the atypical glands have an eosinophilic cytoplasmic change (Photographs contributed by Dr. Kelley Carrick))

define abnormal endometrial tissue based on quantitative pathologic criteria (Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015). The three subcategories include: (1) benign endometrial hyperplasia, (2) endometrial intraepithelial neoplasia, and (3) carcinoma. The pathologic diagnostic criteria of endometrial intraepithelial neoplasia include lesions that have a minimum dimension of 1 mm, increased gland to stroma ratio, a difference in cytology of the lesion as compared to the background tissue, and the exclusion of benign mimics (i.e., polyps, secretory endometrium, effects of exogenous estrogen), and cancerous lesions (Table 1). These criteria can be applied clinically by pathologists or by using formal computerized analysis to assign a D score, which correlates specifically to benign tissue versus EIN. The development of this specific criteria using histomorphologic, genetic, clinical, and biological data attempts to truly differentiate precancerous lesions from benign lesions while maintaining a high degree of sensitivity for detecting precancerous lesions. In a prospective multicenter study using the D score to assign a diagnosis of EIN, the classification system was shown to have a 100 % sensitivity in detecting progression to cancer and a 38 % positive predictive value, compared to the 91 % sensitivity and 16 % positive predictive value of the WHO classification system (Baak et al. 2001). In addition, the EIN system has shown that interobserver reproducibility of the EIN system is greater than the WHO94 (Hecht et al. 2005).

Although the EIN criteria represent a more quantitative classification system than the WHO94 criteria, the latter represent a more widely used classification system. Thus, most studies use the WHO94 classification system when performing analyses, and most of the current knowledge, including epidemiologic risk factors and management strategies, pertain specifically to the four-tier classification of EH. Epidemiology studies of EIN remain limited. The EIN nomenclature and system, however, falls in line with the nomenclature of other precancerous lesions of the gynecologic tract, for example, vulva intraepithelial neoplasia (VIN) or cervical intraepithelial neoplasia (CIN). Currently, the EIN classification system lumps all premalignant lesions into a single category. Current research is attempting to further divide the EIN category into grades or classes, to further delineate which lesions are more severe and to determine which lesions would be responsive to hormonal treatment versus require surgical management (Mutter 2000). Still, the EIN classification system is currently the preferred schema of the American Congress of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists for classifying abnormal endometrial epithelium given the quantitative and reproducible nature of this classification system.

3 Epidemiology

Endometrial hyperplasia mainly effects postmenopausal women and women in their later reproductive years with irregular ovulation. This disorder has historically and most commonly been classified by the WHO criteria, and thus much of the epidemiologic data focus on the subcategories of this classification system. Endometrial hyperplasia affects approximately one out of 1000 women annually (Lacey et al. 2012). This condition is highest in women aged 50–54 and rare in women less than 30 years of age. The incidence of endometrial hyperplasia decreases after the age of 70. In asymptomatic postmenopausal women, the prevalence of endometrial hyperplasia with and without atypia is 0.54 % and 4.86 %, respectively (Gol et al. 2001).

4 Risk Factors

Risk factors for endometrial hyperplasia are generally similar to that of endometrial cancer. There is a strong association with disorders that involve exposure of the endometrium to an increase in either endogenous or exogenous unopposed estrogens. Thus, some of the most notable risk factors include Tamoxifen use, obesity, and polycystic ovarian syndrome (chronic anovulation). Other risk factors include Lynch syndrome, nulliparity and infertility, and diabetes.

4.1 Obesity

Obesity is associated with a higher level of circulating endogenous estrogens, which is secondary to the conversion of androstenedione from adipose tissue to estrone, increased rates of anovulation, and a decrease in circulating sex hormone globulins. There is a proportional relationship between BMI and risk of endometrial hyperplasia. Obese women have approximately six times the risk of endometrial hyperplasia compared to nonobese women (Balbi et al. 2012). In morbidly obese postmenopausal women (BMI $>$ 40), the risk of endometrial hyperplasia with atypia is as high as eightfold. In morbidly obese premenopausal women, this risk is estimated to be as high as 13-fold, possibly suggesting an earlier age of diagnosis in women with obesity (Epplein et al. 2008).

4.2 Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS), an endocrinologic disorder that is associated with chronic anovulation, affects approximately 8–12 % of women of reproductive age (March et al. 2010). Women with PCOS have a threefold increased risk of endometrial cancer (Haoula et al. 2012). Among women with PCOS, the prevalence of endometrial hyperplasia is estimated to be approximately 35–49 %, with a prevalence of approximately 13 % for atypia (Cheung 2001; Tingthanatikul et al. 2006). The association of PCOS with endometrial hyperplasia is thought to be due to chronic anovulation. PCOS is also associated with obesity and diabetes, which are both independent risk factors for endometrial hyperplasia.

4.3 Hormone Replacement Therapy (HRT)

HRT, with either unopposed estrogen or estrogen and progesterone combinations, has been used for decades to combat the unacceptable effects of declining endogenous estrogens in women at the time of menopause. Long-term use of unopposed estrogen for the relief of vasomotor symptoms related to menopause is associated with a 10–20-fold increase risk of endometrial cancer (ACOG 2015). Use of unopposed estrogen as HRT is associated with a 5-fold to as high as 16-fold increase in the likelihood of developing endometrial hyperplasia with high doses or prolonged use (Lethaby et al. 2000). The estimated prevalence of women who use a moderate dose of estrogen alone for up to 3 years is 28 % for simple endometrial hyperplasia, 23 % for complex endometrial hyperplasia, and 11.8 % for endometrial hyperplasia with atypia (Judd et al. 1996). The risk of progression is likely similar to that of any woman in the general population that carries the diagnosis of EH. Addition of progesterone to the HRT regimen greatly reduces the risk of endometrial hyperplasia. Thus, the recommended use of estrogen replacement therapy includes using the lowest dose for the shortest duration possible. In addition, the use of combined progesterone in continuous or cyclic fashion to counteract the proliferative effects of estrogen alone is recommended (ACOG 2015).

4.4 Tamoxifen Use

Tamoxifen is a selective estrogen receptor modulator (SERM), which acts as an estrogen antagonist in breast tissue and thus is used to prevent and treat breast cancer. Unlike other SERMs, such as raloxifene, tamoxifen acts as an estrogen receptor agonist in endometrial tissue, thus its use is associated with an increase in risk of EH and endometrial cancer (approx. 2.5-fold increase in risk) (ACOG 2015). This effect is evident in postmenopausal women rather than premenopausal women (Fisher et al. 2005). The incidence of EH among women with long-term use of tamoxifen is estimated to be 4.4 per 1000 women annually (Runowicz et al. 2011). In women with breast cancer who are treated with tamoxifen and also have a preexisting endometrial hyperplasia, the risk of progression to a higher grade of EH or endometrial cancer is approximately 20 % (Garuti et al. 2006).

4.5 Lynch Syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is a highly penetrant autosomal-dominant condition associated with an increased risk of the early onset of a variety of cancers, including endometrial cancer and colon cancer. The syndrome is characterized by an inherited defect in mismatch repair genes. The lifetime risk of endometrial cancer in women with lynch syndrome is estimated to be as high as 60 % and may exceed the risk of colorectal cancer (Committee on Practice Bulletins- Gynecology and Society of Gynecologic Oncology 2014). Up to 18 % of women with lynch syndrome will develop endometrial cancer prior to the age of 40. Although the risk of endometrial hyperplasia in women with Lynch syndrome is unknown, studies have shown a prevalence of 2.8–4.5 % of EH among women with Lynch syndrome undergoing surveillance screening with endometrial biopsy (Nebgen et al. 2014).

4.6 Reproductive Factors

Nulliparity and infertility have both been shown to be independent risk factors for EH in premenopausal women with abnormal uterine bleeding (Farquhar et al. 1999). Increasing parity is inversely proportional to the risk of EH among premenopausal women (Epplein et al. 2008).

5 Clinical Presentation

The most common clinical manifestation of endometrial hyperplasia is abnormal uterine bleeding (AUB). In women with postmenopausal bleeding, the prevalence of hyperplasia is as high as 15 %, compared to a prevalence of <6 % in asymptomatic women (Espindola et al. 2007). In perimenopausal women with AUB – characterized as prolonged, heavy, or irregular menstrual cycles – the prevalence of endometrial hyperplasia is estimated to be 10–36 % (Ash et al. 1996; Jetley et al. 2013). Depending on the histologic findings, the risk of endometrial hyperplasia progressing to cancer is as high as 29 % and the risk of concomitant endometrial cancer is 42 %. Thus, it is important to perform a diagnostic evaluation in any woman over the age of 45 with postmenopausal bleeding or AUB. In women under the age of 45 with AUB, whether or not to perform a diagnostic evaluation depends on risk factors and clinical suspicion (i.e., risk factors, persistence of symptoms). Occasionally, abnormal endometrial cells can be seen on cervical cytology in asymptomatic women. A finding of adenocarcinoma on cytology requires diagnostic evaluation in all women. Atypical glandular cells on cytology in women greater than 35 years of age or in women less than the age of 35 who are symptomatic (AUB) is a worrisome finding that requires evaluation of the endometrium. Postmenopausal women with endometrial cells on cervical cytology also require diagnostic evaluation of the endometrial cavity. Asymptomatic premenopausal women with findings of benign endometrial cells on cervical cytology do not require further workup (ACOG 2013).

6 Diagnostic Evaluation

The algorithm for diagnostic evaluation for women greater than the age of 45 with a clinical presentation concerning for endometrial hyperplasia is outlined in Fig. 2. Transvaginal ultrasound (TVUS) has a high negative predictive value for endometrial cancer and can be reliably used as the initial test in the diagnostic workup when evaluating a postmenopausal woman with bleeding. In a postmenopausal woman with a endometrial stripe less than or equal to 4 mm, the risk of cancer is less than 1 %. In perimenopausal woman, ultrasound is less useful in ruling out endometrial carcinoma based on EMS; however, it can be used to detect any focal lesion or grossly thickened endometrial stripe (ACOG 2015). Any postmenopausal woman with an EMS of >4 mm or a focal lesion on TVUS requires endometrial sampling with either an endometrial biopsy (EMB) or dilation and curettage (D&C).

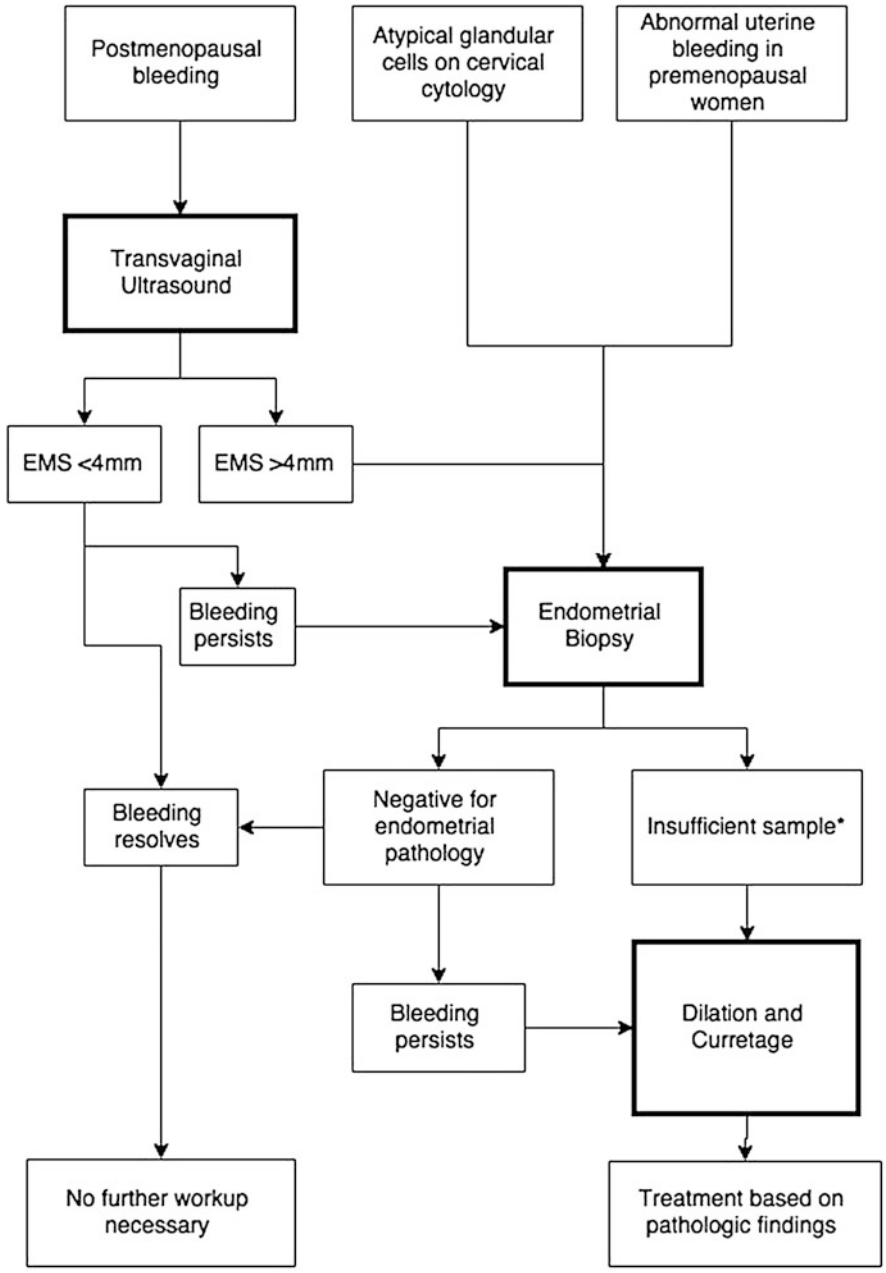

Fig. 2 Algorithm for the diagnostic evaluation for suspected endometrial hyperplasia (*It is reasonable to repeat EMB with one insufficient result. After two insufficient results, dilation and curettage is indicated)

EMB can be performed in the office setting and is the gold standard diagnostic test in the setting of abnormal uterine bleeding and/or abnormal ultrasound findings. Because EMB can be done in an outpatient setting rather than in the OR, several advantages exist for an EMB over a D&C including less procedural time, minimal anesthesia (if any), less cost, need for minimal cervical dilation (if any), and decreased risk of uterine perforation. However, the ability for EMB to detect endometrial disease depends on whether the endometrial disease is focal or global. On

average, EMB samples approximately 4 % of the endometrial surface. Based on a metaanalysis, the endometrial pipelle technique of EMB has a sensitivity of 81 % and a specificity of 98 %, and the detection rates for endometrial cancer in postmenopausal and premenopausal women are 99.6 % and 91 %, respectively (Dijkhuizen et al. 2000). The negative predictive value for detecting endometrial cancer in women with complex atypical hyperplasia is higher for D&C than EMB (69 % vs. 55 %) (Suh-Burgmann et al. 2009). Thus it is not unreasonable to perform a D&C prior to hysterectomy, particularly if it would change surgical management regarding hysterectomy and possible staging strategies if concomitant endometrial cancer were known to exist.

In approximately 4–15 % of women, an EMB will return with insufficient tissue for cytological evaluation. Postmenopausal women or women with a thin EMS have a higher likelihood of insufficient sampling (Elsandabesee and Greenwood 2005; Polena et al. 2007). If an insufficient result is obtained, it is reasonable to either repeat the EMB or proceed with D&C. After two insufficient results, endometrial sampling with D&C is indicated. In a postmenopausal woman, if the EMB is negative but the bleeding abnormality persists, D&C is indicated. The American Congress of Obstetricians and Gynecologists recommends a hysteroscopy with D&C for detection of any focal lesions that may be present (Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015).

7 Management

In a patient who has been newly diagnosed with endometrial hyperplasia or endometrial intraepithelial neoplasia, after concurrent adenocarcinoma has been ruled out, the goal of treatment is prevention of progression to endometrial cancer. Generally, management options include surveillance, medical management, and surgical management. When choosing between these management options, the potential of concurrent malignancy or progression to endometrial cancer, desire to preserve fertility, and surgical candidacy must all be considered. While surgical management is an effective and definitive means of treating higher-risk endometrial hyperplasia in women who have completed childbearing, nonsurgical treatment options are not as well defined for EH.

7.1 Surveillance

Surveillance by serial EMB is a management option for patients with either hyperplasia without atypia (WHO classification) or benign hyperplasia (based on EIN classification). The risk of progression to endometrial cancer for these entities is 1–3 % for hyperplasia without atypia (based on WHO) or 0–2 % for benign hyperplasia (based on EIN classification), respectively (Baak et al. 2005; Kurman et al. 1985). Furthermore, spontaneous regression has been estimated to be approximately 70 % in women with hyperplasia without atypia (Reed et al. 2009). Although not the recommended management option, given the low risk of progression and high rate of regression, it is reasonable to monitor patients who either have a contraindication to progestin therapy or who decline medical/surgical management. These patients should be evaluated by EMB every 3–6 months until normal endometrium is found. There is not a defined time point for declaring failure to regress; however, most studies have shown median time to regression on hormonal management to be approximately 6 months, and therefore 6 months is likely a reasonable window for conservative management as well. Once regression is achieved, it is also worth considering repeat EMB to ensure stability of regression, and it is important to resample the endometrium in the future if abnormal uterine bleeding recurs.

7.2 Medical Management

Medical management involves the use of hormone therapy to reverse EH. It is the first-line treatment in women with hyperplasia without

Table 2 Progestin therapies commonly used for treatment of Endometrial Hyperplasia or EIN

Hormone	Route	Dosage	Comment	Common side effects
Medroxyprogesterone Acetate (MPA)[a]	Oral	10–20 mg daily or cyclic 12–14 days/month	First-line therapy for non-atypical hyperplasia. Cyclic therapy may be superior to continuous	Irregular bleeding, acne, abdominal pain/nausea
Megestrol Acetate (MA)[a]	Oral	40–320 mg daily	More potent than MPA thus usually reserved for women with atypical hyperplasia	Weight gain, abdominal pain/nausea/diarrhea, Insomnia/mood swings, hypertension, alopecia
Micronized progesterone	Vaginal	100–200 mg daily or cyclic 12–14 days/month	For use in women without atypia	
Depot medroxyprogesterone	Intramuscular	150 mg every 3 months	Regressions rates are likely similar to that of oral MPA	Amenorrhea, acne, Weight gain, headache
Levonorgestrel	Intrauterine	20 mcg/day releasing device	Estimated to be more effective than oral therapy.	Amenorrhea, abdominal pain, acne, irregular bleeding (first 90 days after insertion)

[a]Regression rates overall for oral progestin therapy based on systematic review is 66–69 %. These regimens have been shown to have poor compliance compared to the IUD (Armstrong et al. 2012; Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015; Gallos et al. 2010; Guven et al. 2001; Trimble et al. 2012)

atypia or benign hyperplasia as, again, the risk of progression to cancer is low. In women with atypical hyperplasia or EIN, medical management is acceptable in patients who wish to preserve fertility or who are poor surgical candidates. In women desiring to spare fertility, the goals of management are complete clearance of the disease, return of normal endometrial function, and prevention of invasive endometrial cancer. In patients who are poor surgical candidates (i.e., elderly patient with multiple comorbidities), the goals of management include disease stabilization and risk reduction of developing endometrial cancer.

Progestin is the most commonly used hormone to treat EH. In normal endometrium, progesterone counterbalances the endometrial proliferation caused by estrogen and stimulates secretory differentiation (Kim and Chapman-Davis 2010). In precancerous lesions, the mechanism by which progesterone is therapeutic involves apoptosis in neoplastic endometrial glands associated with tissue sloughing during withdrawal shedding, as well as activation of progestin receptors, which leads to stromal decidualization and thinning of the endometrium (Kim and Chapman-Davis 2010). When used to treat EH, progestins have an impact on the endometrial lining as early as 10 weeks after initiation.

Progestin has been shown to be clinically effective in treating endometrial hyperplasia in a variety of routes, doses, and formulations (Table 2) A pooled analysis has estimated regression rates with use of oral therapy to be 66–69 % (Gallos et al. 2010). Medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are the most common progestin therapies. MA is known to be more potent than MPA, thus MA is typically used as first line in women with EH with atypia. In one prospective study, regression rates with the use of MA were as high as 90 %. MPA may be administered via oral or intramuscular routes. Studies comparing various routes and formulations of oral progestin therapy have been inconclusive, thus an optimal regimen has not been determined. However, multiple single arm and retrospective studies of progestin-based therapies have been conducted and have been deemed acceptable for use (of any of the aforementioned regimens). Limited data exists for the use of vaginal

progesterone in endometrial hyperplasia; however, the estimated regression rate is 90 % in women with simple and complex hyperplasia without atypia (Affinito et al. 1994). For reproductive aged women without a contraindication to estrogen, combined oral contraceptives (COC) may be used, though these are typically used to manage women with EH without atypia. COCs are estimated to reduce the risk of endometrial cancer by approximately 50 %.

In addition to systemic hormone therapy, the levonorgestrel-releasing intrauterine device (IUD) provides a feasible and possibly superior alternative to oral therapy. The local acting progesterone has a stronger effect on the endometrium while having lower systemic progesterone levels, reducing the incidence of side effects. The estimated regression rates for non-atypical and atypical hyperplasia with the use of the levonorgestrel IUD are 90 % and 96 %, respectively (Gallos et al. 2010). A recent metaanalysis comparing the levonorgestrel IUD with oral progesterone therapy suggest that the IUD is approximately three times as effective as oral progestin therapy with continual use for 6 months (Abu Hashim et al. 2015).

The median time to regression in most studies, defined by a biopsy revealing normal endometrium, is approximately 6 months, after which if abnormal endometrium still exists, treatment failure is probable (Mentrikoski et al. 2012). Progestin therapy should be continued for at least 12 months in women who do not desire pregnancy or until progression is identified. In women who desire pregnancy, oral progestins should be continued for 3–6 months or until EH is no longer found on endometrial biopsy.

Endometrial sampling can be performed via EMB and is usually performed at 3–6 month intervals. EMB can be performed with an IUD in place. D&C can also be performed for surveillance and is usually repeated every 3–6 months. EMBs generally can be done in the office whereas D&C's frequently require the operating room. For women who have a persistent or progressive lesion, surgical management should be considered on an individual basis.

7.3 Surgical Management

Total hysterectomy with or without bilateral salpingo-oophorectomy (BSO) is the most effective treatment for either atypical hyperplasia (AH) or EIN and provides definitive assessment of a possible occult carcinoma. Independent risk factors for concurrent endometrial cancer include age, obesity, and complex hyperplasia with atypia (Matsuo et al. 2015). Thus, this treatment option is the standard of care for EIN or AH in women who are done with childbearing, especially those with the aforementioned risk factors. Hysterectomy is also indicated in patients with EH with or without atypia if medical management has failed. Hysterectomy is curative for patients with a final postoperative diagnosis of endometrial hyperplasia.

Surgical approaches include abdominal, vaginal, and minimally invasive approaches with laparoscopic or robotic technique. All modalities are acceptable and depend on clinical and patient-specific factors, as well as the skill of the surgeon and the extent of the procedure. For example, clinical patient factors such as complex anatomy, uterine size, body mass index, and prior surgical history should all be considered when determining route of hysterectomy. Currently, vaginal hysterectomy is recommended as the preferred route for performing hysterectomy for nonmalignant conditions (Aarts et al. 2015). However, it is important to note that it may be technically difficult to perform a BSO from a vaginal approach, and surgical staging (i.e., retroperitoneal lymphadenectomy) cannot be performed. It is also preferred that the hysterectomy not require any form of morcellation or deconstruction of the uterus as it may disrupt proper evaluation of the endometrium, particularly when looking for occult cancer and may potentially cause iatrogenic metastases if cancer were present. Thus uterine size must be accounted for if considering a vaginal or minimally invasive approach (which typically requires delivering the uterus through the vagina).

If endometrial cancer is identified, one must also consider the strategy for surgical staging. In general, it may be challenging to diagnose occult endometrial cancer on intraoperative uterine

analysis or frozen section. In one study, the negative predictive value for identifying endometrial cancer in patients with complex hyperplasia with atypia was only 73 % (Morotti et al. 2012). Thus it is possible that over one quarter of patients who have endometrial cancer may not be detected by use of frozen section. Therefore, it is generally most effective to identify endometrial cancer in formalin fixed paraffin embedded tissue rather than by frozen section assessment. Surgeons may worry that the patients would then require a second surgery if endometrial cancer were identified on the permanent analysis of the hysterectomy specimen. However, the majority of these occult endometrial cancers are low grade, early stage cancers, which do not necessarily require lymphadenectomy; simple hysterectomy would be considered complete and definitive treatment. The premise of this staging strategy is based on a schema developed at the Mayo clinic, by which endometrial cancer cases of low grade (1–2), less than 2 cm tumor diameter on intraoperative evaluation and less than 50 % myometrial invasion by frozen section, do not require lymphadenectomy, as the chance of identifying metastases is about 1 % or less (Bogani et al. 2014; Mariani et al. 2000, 2008)

Whether or not to perform a bilateral salpingo-oophorectomy (BSO) depends on the presence or absence of endometrial cancer, patient characteristics, and presence of a primary indication for BSO. There is ovarian involvement in approximately 5 % of endometrial cancer cases and BSO is indicated in known endometrial cancer cases. However, there are no current standardized recommendations about whether or not to perform a BSO for EH. In general, it has not been required. However, in most cases, there is relatively low surgical risk to performing a BSO. That being said, if a vaginal hysterectomy is performed, a separate abdominal approach either open or minimally invasive may be required to access the adnexa located high on the pelvic brim and complete the BSO. In postmenopausal women, it is reasonable to perform a BSO. In premenopausal women, however, risks of BSO including possible loss of bone density, increased cardiovascular events, and early onset of menopausal symptoms including hot flashes, decreased libido, and disrupted sleep patterns must be considered. Thus, in premenopausal women, BSO at the time of hysterectomy is not required unless there are other indications for removal of the ovaries. This must be considered against the risk of needing a separate surgery in the future for BSO.

Supracervical hysterectomy is contraindicated in patients with endometrial hyperplasia or EIN. The American Congress of Obstetricians and Gynecologists recommends against this approach because of concerns for underlying malignancy, which can reside in the lower uterine segment (ACOG 2007; Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015). Hyperplasia can also reside in the lower uterine segment and there is risk of retained endometrium with supracervical hysterectomy. Morcellation and endometrial ablation are absolutely contraindicated in the surgical management of endometrial hyperplasia as morcellation has been associated with spread of occult cancers and endometrial ablation has an unknown effectiveness in treatment for hyperplasia because it is difficult to assess the endometrial lining after this procedure is performed.

8 Screening and Prevention

There currently are no recommendations for routine screening for endometrial hyperplasia (or endometrial cancer) in the asymptomatic general population. Lifestyle modifications, prophylactic medical management, and/or prophylactic surgery are indicated for some patients based on risk factors. In obese women or women with diabetes, lifestyle modifications such as diet, exercise, and weight loss, are recommended. In women with diabetes, glucose lowering agents such as metformin may decrease the risk of EH or endometrial cancer, although the evidence remains very preliminary and controversial and is limited to retrospective studies. In women with chronic amenorrhea or PCOS, progestin therapy can be used to lower the risk of development of EH or endometrial cancer. When hormone replacement therapy is indicated, the addition of

progesterone to the estrogen regimen will reduce the risk of EH associated with HRT, and thus all women who retain a uterus should receive combination hormonal replacement therapy and not estrogen alone.

The prevalence of EH among women with ER positive breast cancer is estimated to be 7 %. Therefore it is reasonable to screen women for preexisting endometrial pathology prior to the initiation of tamoxifen therapy (Garuti et al. 2006). Any woman that is to initiate tamoxifen therapy should be informed of the effects that tamoxifen may have on the uterus. They should be counseled appropriately and the importance of reporting any abnormal vaginal symptoms, specifically abnormal bleeding, should be evaluated (ACOG 2014). In women with lynch syndrome, endometrial biopsy every 1–2 years starting at age 30–35 years is recommended. In a multicenter, retrospective, case control study, the risk of endometrial cancer in women with lynch syndrome was significantly reduced from 33 % to 0 % with a prophylactic hysterectomy; therefore, risk-reducing surgery should be recommended to any woman with lynch syndrome that is done with childbearing (Committee on Practice Bulletins-Gynecology and Society of Gynecologic Oncology 2014; Schmeler et al. 2006).

9 Conclusion

It is critical for all gynecologic clinicians to understand diagnosis and management of EH. This precursor to endometrial cancer can be easily diagnosed based on clinical symptoms with minor gynecologic procedures. When detected, progression to invasive endometrial cancer can often be effectively reduced using progestin therapy with close follow-up and surveillance. Endometrial hyperplasia frequently resolves with hormonal treatment and is definitively cured with hysterectomy. In a small proportion of cases, concurrent endometrial cancer may be diagnosed on the final hysterectomy specimen. Fortunately, most cases of concurrent endometrial cancer are typically of early stage and low-grade histology, which bears a very favorable prognosis even with hysterectomy alone. Treatment for EH should account for individualized characteristics (i.e., desire to preserve fertility, surgical candidacy), risk factors, severity of the lesion, and persistence or progression of the lesion or clinical symptoms. Patients and providers should discuss all these aspects of EH in order to manage the condition effectively.

10 Cross-References

- ▶ Benign and Malignant Pathology of the Endometrium
- ▶ Conservative Management for Endometrial Cancer
- ▶ Diagnosis and Management of Postmenopausal Bleeding
- ▶ Impact of Obesity on Gynecological Diseases
- ▶ Management of Abnormal Uterine Bleeding in the Late Reproductive Years

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Conservative Management of Endometrial Cancer

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Abstract

Endometrial cancer is the most common gynecologic malignancy in the United States. Approximately 54,000 new cases will be diagnosed in 2015, and the incidence of endometrial cancer has increased by 1.5 % per year among women younger than 50 years, and by 2.6 % per year among women 50 years and older. Fortunately, the overall mortality due to endometrial cancer remains low (ACS. American Cancer Society facts & figures 2015. American Cancer Society; 2015). Endometrial cancer is standardly treated with surgical resection via total hysterectomy (removal of the uterine corpus and cervix) and bilateral salpingo-oophorectomy, with or without lymph node assessment. However, given the rise in incident endometrial cancers largely related to the obesity epidemic, increasing numbers of young women with endometrial cancer will desire to preserve the uterus for fertility, and opt for conservative management. At the other end of the spectrum, a subset of patients with endometrial cancer may be unsuitable surgical candidates largely due to obesity and its related comorbid conditions and physical dysfunction. Both of these patient populations present a challenging management dilemma because surgery may not be a primary treatment option. Instead, conservative management of endometrial cancer based largely on hormonal therapy may be considered. While this approach is not standard of care, there is increasing evidence supporting the safety and efficacy of conservative therapy, particularly for low-grade, early stage endometrial cancers. This evidence, however, must be tempered by the relative high recurrence rates and goal of subsequent hysterectomy when feasible.

Keywords

Fertility sparing • Conservative management • Hormonal therapy • Progesterone

1 Introduction to Conservative Management

The most common reasons for conservative management of endometrial cancer are dichotomous: desire for fertility preservation or comorbidities and functional status that are not compatible with surgery. Primary conservative management of endometrial cancer with hormonal therapy is a newer concept; however, the biologic principle is not. Hormonal therapy has been utilized dating back to the 1960s for the management of metastatic endometrial cancer. Specifically, Drs. Kelley and Baker used progestins to treat patients with metastatic and/or symptomatic endometrial cancer. The majority of patients showed regression of disease, and most reported symptomatic relief. Responses were particularly seen in women with well-differentiated endometrial cancer (Kelley and Baker 1965). Using largely the same biologic principles, conservative treatment for endometrial cancer has been reported dating back to 1959 with use of different progesterone formulations (Kistner 1959). More recently, several small to moderate-sized studies have reported efficacy in hormone-based conservative management of endometrial cancer (Gallos et al. 2012; Park et al. 2013; Ushijima et al. 2007; Park et al. 2013b). While surgery remains the mainstay of endometrial cancer treatment and primary medical management remains controversial, mounting evidence support these novel therapies.

2 Epidemiologic Considerations

2.1 Age: Young Women with Endometrial Cancer

Up to 14 % of endometrial cancers occur in women of childbearing age, and the incidence of endometrial cancer continues to rise: recent data show 1.5 % increase per year among women younger than 50 years, and 2.6 % increase per year among women 50 years and older (ACS 2015). Younger women with endometrial cancer are typically obese, often nulliparous, and have

history of menstrual irregularities including those related to polycystic ovarian syndrome, anovulation, or metabolic syndrome. These patients are usually detected due to infertility or bleeding complaints. While the youngest endometrial cancer patients are often better surgical candidates, their desire to maintain fertility, particularly to carry their own pregnancy, precludes hysterectomy. Fortunately, the majority of young women with endometrial cancer have the less aggressive subtypes, characterized by low-grade histology and early stage disease.

2.2 Age: Older Age and Comorbidities

Several differences exist in the clinical and pathologic profile of older compared to younger endometrial cancer patients. Not surprisingly a great majority of older women with endometrial cancer have one or more comorbidities, and comorbidities increase with age in the general adult population. In general, women with endometrial cancer have been found to have higher rates of comorbidities, namely, at least one and half times the risk for congestive heart failure, hypertension, or pulmonary disease; twice the risk of diabetes; and over three times the risk for obesity (Kurnit et al. 2015). Rates of hypertension and diabetes have been reported to be 25–58 %, and 24–26 %, respectively, in endometrial cancer patients (Ko et al. 2014; Kurnit et al. 2015). Furthermore, increased age at diagnosis has been associated with higher likelihood of hypertension and diabetes (Kennedy et al. 2000; Saltzman et al. 2008), and higher Charlson comorbidity scores (Truong et al. 2005). Somewhat paradoxically, the oldest women with endometrial cancer have been found to be less severely obese (Bittoni et al. 2013) which may be in part due to differences in the biology of disease, lending to a higher prevalence of more aggressive subtypes of endometrial cancer in women of older age.

2.3 Obesity and Endometrial Cancer

Obesity is a rising epidemic in many parts of the developed world. Current data drawn from the 2011–2012 United States NHANES (National Health and Nutrition Examination Survey) revealed that 58.5 % of nonpregnant women aged 20–39 years were overweight or obese, 31.8 % obese, and 8 % extremely obese. Of women aged 40–59 years old, 71.7 % were overweight or obese, 39.5 % obese, and 9.8 % extremely obese (Ogden et al. 2014). Given that well over half of all women in the United States are overweight or obese, obesity-related health conditions including endometrial cancer are only expected to increase (Fig. 1).

Renehan et al. showed that a 5 kg/m^2 increase in BMI was strongly associated with endometrial cancer (OR 1.59, $p < 0.001$) (Renehan et al. 2008). Accordingly, Reeves et al. predicted that up to 51 % of endometrial cancer cases could be attributable to obesity (Reeves et al. 2007). Nevadunsky et al. report a strong correlation between obesity and younger age at diagnosis, and Duska et al. found that women aged 24–40 years and BMI >30 were associated with stage I, grade I disease (Duska et al. 2001; Nevadunsky et al. 2014). In general, obesity induces a hyperestrogenic state due to the conversion of adrostenedione to estrone in peripheral adipose tissue. Thus, obesity has been associated with estrogen-dependent endometrial cancers, classically referred to as the common, type I endometrial cancer. However, it appears that obesity may also be associated with type II endometrial cancers. Drawing upon the pooled analysis by the Epidemiology of Endometrial Cancer Consortium, 75 % of all type I and 61 % of all type II patients were overweight or obese (Setiawan et al. 2013), and similar high rates were found in prospectively enrolled endometrial cancer patients in a national trial as well as smaller multi-institutional studies (Ko et al. 2014).

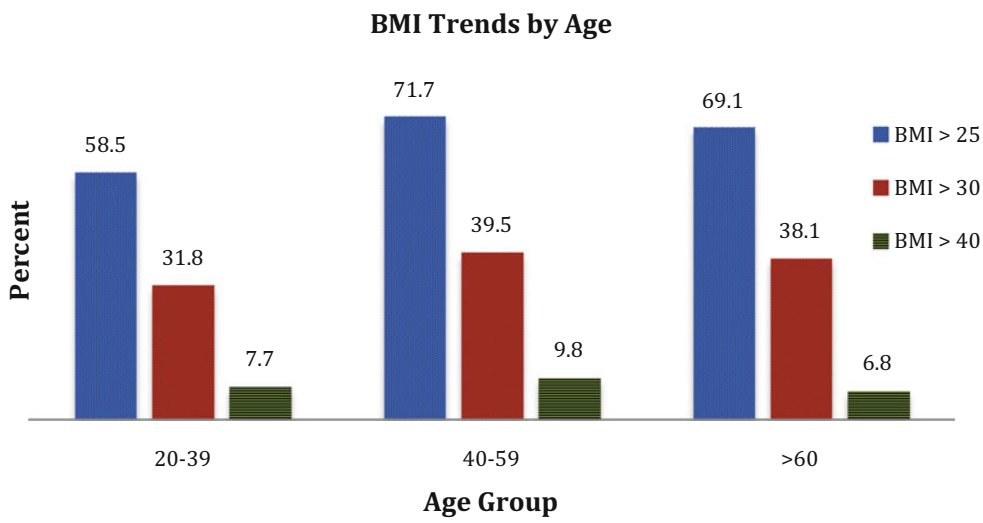

Fig. 1 Obesity category by age group in American women (Data adapted from Ogden et al. (2014))

2.4 Special Populations: Hereditary Syndromes

While endometrial cancer has not been classically thought of as a heredity-based cancer, there is a subpopulation of endometrial cancer patients that do develop endometrial cancer as a result of a genetic syndrome. These include patients with Lynch syndrome, which may account for approximately 5 % of endometrial cancer cases. Lynch syndrome, also referred to as hereditary nonpolyposis colorectal cancer, is an autosomal dominant condition characterized by having a germline mutation in one of four mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) with an inherited propensity to develop colon, endometrial, ovarian, genitourinary, and gastric cancers. Women with Lynch syndrome have a lifetime risk of 15–66 %, depending on the type of MMR mutation, for developing endometrial cancer and the risk increases sharply after age 40, with the median age of diagnosis of 46 (Bonadona et al. 2011; Burke et al. 2014b). The identification of patients with Lynch syndrome has previously depended on clinical suspicion and inquiry into a detailed family history of a patient newly diagnosed with colon cancer based on the Bethesda and Amsterdam criteria (Matthews et al. 2008) (Table 1).

Table 1 Amsterdam criteria

Amsterdam criteria: familial risk for Lynch syndrome or hereditary nonpolyposis colorectal cancer[a]
Minimum 3 relatives with an HNPCC-associated cancer
1. One first-degree relative of the other 2 relatives
2. At least 2 successive generations are affected
3. At least 1 relative diagnosed before age 50
4. Must exclude familial adenomatous polyposis
5. Tumors verified by pathological examination

[a]Approximately half of all patients meeting listed criteria will have Lynch syndrome. Importantly, many families with Lynch syndrome will not meet these criteria

According to Lindor et al., approximately half of women meeting Amsterdam criteria will have Lynch syndrome (Lindor et al. 2006). While colorectal cancers are commonly expected sentinel events, more than 50 % of women with Lynch syndrome will present with gynecologic malignancy first (Lu et al. 2005). For women with newly diagnosed endometrial cancer, immunohistochemistry (IHC)-based screening off of paraffin-embedded tissue has been found to have a higher detection rate of identifying Lynch syndrome affected patients than (especially in those age <60), compared to MSI testing, family history assessment, or tumor morphology testing (Ferguson et al. 2014). Subsequently, multiple

other investigators have reported on the success of tissue-based screening algorithms using IHC assays for non-normal expression of mismatch repair genes in newly diagnosed endometrial cancer patients (Buchanan et al. 2014; Frolova et al. 2015; Mills et al. 2014). Dating back to 2007, the Society of Gynecologic Oncologists (SGO) had made formal recommendations to screen all women diagnosed with endometrial cancer under the age of 60 using IHC (Lancaster et al. 2007). Currently, the National Comprehensive Cancer Network Guidelines for the Management of Endometrial cancer suggests screening with IHC and microsatellite instability assays for inherited mismatch repair gene mutations in three patient populations: 1. Patients with newly diagnosed endometrial cancer under the age of 50, 2. Patients with a significant family history of endometrial and/or colorectal cancer, 3. Patients with epithelial tumors (rather than those with stromal/mesenchymal endometrial tumors) (NCCN 2015). Thus, patients diagnosed with endometrial cancer, particularly those who are premenopausal and of younger age, should be assessed for Lynch syndrome by IHC and/or referral to a genetic counselor. Determination of whether they are Lynch syndrome carriers may alter decisions about treatment and fertility desires.

Currently, the impact of the mismatch repair gene mutations in Lynch syndrome patients on cancer persistence, progression, and recurrence remains unknown. Conservative management of endometrial cancer in these cases may be considered using similar criteria as for non-Lynch syndrome patients; however, since Lynch syndrome patients also have an elevated lifetime risk for developing ovarian cancer of up to 24 %, bilateral salpingo-oophorectomy at the time of definitive surgery for uterine cancer should be considered. The increased propensity to develop both uterine and ovarian cancer frequently sway both patients and physicians toward definitive surgical management sooner rather than later. Importantly, Lynch syndrome patients need expanded surveillance for other cancers including colorectal, genitourinary, and to a lesser extent, upper gastrointestinal.

Other genetic syndromes such as Cowden's and BRCA-associated hereditary syndromes contribute to fewer overall cases of endometrial cancer, but bear mentioning. Cowden's is an autosomal dominant condition characterized by a mutation in the PTEN tumor suppressor gene. The lifetime risk of endometrial cancer in women with Cowden's is 13–19 %. The association between endometrial cancer and women with BRCA gene mutations remains controversial. While it is clear they have significantly increased lifetime risk of breast and ovarian cancer, data for endometrial cancer are mixed. One smaller case control study reported an association between BRCA2 mutation carriers and uterine serous carcinoma; however, other studies have not replicated these findings. More recently, a large prospective study of patients with BRCA1 and 2 mutations found an increased rate of endometrial cancer; however, this risk was attributable to Tamoxifen use, rather than the BRCA mutation itself (Beiner et al. 2007). Ultimately, a detailed family history should be taken for all cancer patients, and especially for patients diagnosed with premenopausal endometrial cancer.

3 Ideal Candidates for Conservative Management

3.1 Endometrial Cancer Classification

Endometrial cancer has classically been divided into two major categories: type I and type II, based on clinical pathologic differences. Type I endometrial cancers are typically associated hyperestrogenic or unopposed estrogenic states. Clinical characteristics of these patients frequently include obesity, nulliparity, and metabolic syndromes such as diabetes and PCOS (Bokhman 1983). Additionally, type I endometrial cancer typically presents with low-grade endometrioid histology (grade 1 and 2) and is diagnosed at early stage (stage I and II). As a result, women with type I endometrial cancer may be candidates for conservative management as these cancers are

considered less aggressive, detected early, well differentiated, and sensitive to hormonal therapy.

In contrast, type II endometrial cancers are considered less driven by estrogen, less responsive to hormonal management, and generally more aggressive with higher grade histology and advanced stage at diagnosis. Patients with type II endometrial cancer are not typically offered conservative management as the risks of delayed surgical management almost always outweigh the benefits. Fortunately, type II endometrial cancers are typically diagnosed in older postmenopausal women and not frequently seen in women who are still seeking fertility-sparing procedures.

The abovementioned classification system is evolving, and there is a movement toward categorizing endometrial cancer into "low risk" versus "high risk" cases. Low risk has been defined by low-grade histology and early stage presentation, whereas "high risk" has been associated with high-grade histology (grade 3 histology of any histologic subtype: endometrioid, serous, clear cell, undifferentiated) (Brinton et al. 2013; Setiawan et al. 2013).

3.2 Selection of Low Risk Cases

Whereas conservative management was once geared toward patients with advanced disease or recurrence, fertility preservation for younger patients now represents a larger proportion of women diagnosed with endometrial cancer who do not undergo hysterectomy. One major principle exists for women desiring conservative management for endometrial cancer: they must carry a low risk diagnosis. Low risk is defined as having grade 1–2 histology, typically of the endometrioid subtype, less than 50 % myometrial invasion based on MRI imaging, and no evidence of metastatic disease. Previous studies have shown that these patients carry a risk for pelvic and paraaortic lymph node involvement of less than 10 % (Creasman et al. 1987). Various algorithms have been proposed for identifying individuals with low risk of having metastatic disease. One of the most common, proposed by Mariani et al., uses intraoperative frozen section protocol of hysterectomy-based pathology assessment. This study from the Mayo Clinic showed low incidence of nodal metastases (5 %) in patients with $<$50 % myometrial invasion, grade I/II preoperative histology, and endometrioid type endometrial cancer (Mariani et al. 2000). Obviously in conservative management of endometrial cancer, hysterectomy-based assessments cannot be used. However, many physicians have largely applied the same principles (minimal myometrial invasion, small tumor size, and low-grade histology) using imaging and biopsy results to select candidates for conservative management of endometrial cancer. The most ideal patient characteristics of women considering conservative management for fertility-sparing purposes are listed in Table 2.

Table 2 Ideal characteristics for patients electing to pursue conservative management of endometrial cancer

Ideal candidates for conservative management
Well-differentiated endometrial carcinoma – grade 1–2
No myometrial invasion
No extrauterine involvement (metastases, ovarian involvement, lymph nodes)
Strong desire for fertility sparing
Informed consent regarding standard of care (hysterectomy) and acceptance of risks

The above parameters are minimum requirements for conservative management to be feasible. Other considerations include patient compliance and ability to follow-up for surveillance on at least biannual basis. The converse scenario involves inoperable patients whose advanced disease, distant metastases, and/or many comorbidities make them poor surgical candidates. Conservative management in these cases refers to palliative and symptom-controlling regimens involving radiation, chemotherapy, progestin therapy, or a combination of the three.

3.3 Pretreatment Evaluation: Diagnosis and Testing

The ability to provide medical management to an endometrial cancer patient hinges on accuracy in diagnosis. Tissue studies based on endometrial

biopsy or dilation and curettage (D&C) samples are the primary sources for histology grading. With multiple methods of endometrial sampling available, however, a great deal of research has focused on utility of in-office versus surgical methods. A meta-analysis of more than 40 studies found that Pipelle EMB was the best device in both postmenopausal and premenopausal women, with a sensitivity of 99.6 % and 91 %, respectively (Dijkhuizen et al. 2000). A major shortcoming of this study, however, was that only 27 % of studies compared their sampling method of choice to final pathology on hysterectomy. The remaining made comparisons to D&C histology. A more recent study showed that in patients with a preoperative diagnosis of FIGO grade 1, EMB using Pipelle had twice the rate of upgrade on final pathology (17.4 % vs. 8.7 %) (Leitao et al. 2009). Importantly and fortunately, the vast majority of upgrades were from grade 1 to 2 rather than 2 to 3 (16 % vs. 1.7 %); thus, these patients remained in the low or intermediate risk groups. Their group recommended that D&C be used in patients desiring fertility preservation as it offers more accurate diagnosis and is potentially therapeutic (15 % had no residual carcinoma at hysterectomy) (Leitao et al. 2009).

3.4 Determining Extent of Disease

When selecting candidates for fertility-sparing conservative management of endometrial cancer, assessment for myometrial invasion is also extremely important, and this is dependent on imaging. Magnetic resonance imaging (MRI) is currently considered the most accurate tool for prediction myometrial invasion. T2-weighted imaging has a pooled sensitivity and specificity of 87 % and 58 %, respectively, while dynamic contrast-enhanced MRI has a pooled sensitivity and specificity of 81 % and 72 %, respectively, in the assessment of myometrial invasion (Kim et al. 1995). Transvaginal pelvic ultrasound has generally not been recommended for evaluation of myometrial invasion. Its greatest utility is to assess for abnormally thickened endometrial stripes (>4 mm) in postmenopausal women, but in premenopausal women the endometrial thickness is much harder to correlate to potential malignant pathology due to the extensive variation of endometrium through menstrual cycling (Burke et al. 2014b). Computed tomography (CT) shows greatest utility for detection of metastatic disease to the peritoneal cavity and abdominal and pelvic lymphadenopathy and is not recommended for assessment of myometrial invasion. In a meta-analysis of imaging techniques for endometrial cancer, the sensitivity for detecting myometrial invasion was best for contrast-enhanced MRI (80–100 %), in comparison to 40–100 % for CT and 50–100 % for ultrasound (Kinkel et al. 1999). In summary, the National Cancer Center Network (NCCN) and Society of Gynecologic Oncology recommend MRI for evaluation of myometrial invasion in conservative management. Newer technologies including MRI combined with metabolomics and MR-PET are currently being evaluated in clinical trials.

Blood serum assays have not typically been used as selection criteria to identify candidates for conservative management of endometrial cancer. Some investigators have evaluated the utility of elevated CA-125 levels in the management of endometrial cancer, particularly to assess for metastatic disease with high-grade histologies, or as a factor in preoperative models to predict lymph node metastases (Kang et al. 2012). However, given the low specificity of CA-125 due to potentially abnormal values related to any number of conditions (gynecologic and nongynecologic, benign, or malignant), this test is unlikely to yield reliable results and not recommended.

Candidates for fertility-sparing conservative management of endometrial cancer are largely selected based on endometrial sampling, imaging, and clinical patient factors and do not require further surgical assessment. Some individuals, however, have preferred to also perform diagnostic laparoscopy to verify no extrauterine disease prior to initiation of conservative management (Mazzon et al. 2010; Minig et al. 2011; Shan et al. 2013).

4 Treatment Options

4.1 Hormonal Therapy

Conservative management is naturally divided into two groups: fertility-sparing candidates and patients whose medical comorbidities or advanced cancer stage have rendered them inoperable. Here we will focus on fertility-sparing treatment of endometrial cancer. The majority of low-grade endometrioid adenocarcinoma, characterized by well-differentiated tumor cells, are more likely to express progesterone receptors. The GOG 81 trial showed that progestins are more effective in differentiated (low-grade) endometrial cancers than in undifferentiated (high-grade) histologies (Lentz et al. 1996). As a result, most therapies for conservative management of endometrial cancer have been some form of progesterone. Progestin is the synthetic analog (generally administered by pill form) to the naturally synthesized progesterone in the body. The mechanism of action of progestins is downregulation of estrogen receptors, activation of enzymes involved in estrogen metabolism, and cell cycle regulation of cyclin-dependent kinase pathways (Park and Nam 2015).

Oral progesterone-based agents are the most widely studied therapy for conservative management, and the most commonly used agents include medroxyprogesterone acetate (MPA) and megestrol acetate (MA). MPA is typically dosed at 200–800 mg/day (in divided doses), but doses ranging from 2.5 to 1500 mg/day have been studied. MA is most often dosed at 160 mg/day (in divided doses) with reported doses ranging from 16 to 320 mg/day (Gallos et al. 2012). There remains no consensus on optimal dosing of oral progesterones. Park et al. compared high-dose MPA and MA ($\geq$500 mg/day) to low dose ($<$500 mg/day), and found no difference: 77 % versus 79 % complete response ($p = 0.775$) for low and high doses, respectively (Park et al. 2013a). The length of therapy is also a subject of debate. The reported minimum duration for oral therapy is generally 3 months, even if histologic response is documented prior to this time. Three to 6 months appears to be the most common duration of treatment, while 12 months duration is reported in several studies (Burke et al. 2014a; Gallos et al. 2012).

More recently, the levonorgestrel IUD (LNG-IUD) has also been used in fertility-sparing treatment of endometrial cancer with reported complete response rates ranging from 40 % to 100 %. Benefits of using the LNG-IUD include compliance (compared to daily pills), minimal side effects compared to oral progesterone (particularly gastrointestinal and mood), and direct delivery or higher dose progesterone directly to the endometrium. Minig et al. used the LNG-IUD in combination with monthly GnRH analog injections and showed a 57 % complete response for endometrial cancer patients at 1 year of treatment (Minig et al. 2011). Pronin et al. showed even better results with 72 % complete response using LNG-IUD and monthly goserelin injections (Pronin et al. 2015).

As with any intervention, side effect profile should be considered. Oral progestins and GnRH analogs have generally mild, though well-documented side effects including headache, menstrual prodrome symptoms, weight gain, and thrombophlebitis. The LNG-IUD carries a similarly mild profile including menstrual irregularities (amenorrhea or irregular uterine bleeding), pain at placement, and expulsion.

The newest agents under investigation include gonadotropin-releasing hormone agonists (Lupron), aromatase inhibitors (i.e., anastrazole), and inhibitors of mammalian target of rapamycin (mTOR) inhibitors (rapamycin, temsirolimus, everolimus). Additionally, inhibitors of phosphatidylinositol 3-kinase (PI3K), NDA-dependent protein kinase, and VEGF inhibitors (i.e., bevacizumab, aflibercept), and metformin are being investigated (Dedes et al. 2011; Park and Nam 2015). However, trials to date have been largely performed in women with recurrent or advanced EC, and these agents have not been investigated in frontline treatment for fertility-sparing therapy for EC except for a couple case reports. Current clinical trials include the following: LNG-IUD with MPA; MA with metformin versus MA alone; LNG-IUD with

everolimus versus LNG-IUD alone; everolimus plus letrozole versus progestins; and the mTOR inhibitor temsirolimus.

4.2 Nonhormonal and Combination Modalities

Primary hysteroscopic resection followed by oral agents or LNG-IUS, though not studied extensively, is gaining attention. Results thus far have been promising with complete response rates ranging 57–100 % and relapse rates which are often lower than with progestins alone (4–11 %). These small series have all used similar surgical technique: resection of tumor, resection of endometrium adjacent to the tumor, and resection of the myometrium underlying the tumor. If no myometrial invasion was found on final pathology, the women were treated with hormonal therapy (Kalogera et al. 2014; Mazzon et al. 2010; Shan et al. 2013). Some have voiced concerns regarding potential intrauterine adhesions (with repeated instrumentation of the uterine cavity) leading to subsequent infertility; however, these small series have not been able to provide sufficient case numbers to make this assessment.

A novel regimen of photodynamic therapy (PDT) has been tried in endometrial cancer treatment. PDT uses a nontoxic light-sensitive compound that destroys cancer cells by producing active oxygen species when a light-sensitive compound applied to the tissues are exposed to a specific wavelength of light. Treatment of endometrial cancer with PDT has been reported in a small series of 16 patients (11 with primary treatment and 5 with secondary treatment after failure of hormonal therapy), with a response rate of 75 % and a recurrence rate of 33 % (Choi et al. 2013). Given these favorable results, PDT may represent a viable alternative to oral therapy which often requires several months of treatment to produce regression. This intervention, however, warrants significantly more research before it can be recommended as first line treatment.

4.3 Definition of Response

The definitions of response, failure, and progression are important to define. The literature separates responses into complete and partial: complete response is generally defined as reversion to normal endometrium with no hyperplastic or cancerous characteristics. Partial response has been defined as remaining hyperplasia or atypia with degeneration and atrophy of endometrial glands. Progressive disease is diagnosed when repeat sampling shows an upgraded histology (Ushijima et al. 2007). Durable complete response has been defined by some investigators as complete initial response with no later recurrence (Bakkum-Gamez et al. 2012). There is some variation in these definitions and some investigators have defined complete regression sufficient if simple hyperplasia or complex hyperplasia without atypia is found.

The time period for determining a patient's particular response is another topic for which there is no firm answer. Park et al. suggest that 3 months may be sufficient for diagnosis of treatment failure. Other investigators have reported a median treatment time needed for disease regression of 4–6 months, with potentially longer treatment needed in the more obese and anovulatory patients (Kalogera et al. 2014). A patient with no change in histology could continue treatment up to 12 months, while any patient with histologic evidence of progression should proceed to surgical management (Park and Nam 2015).

5 Oncologic Outcomes

The majority of women who undergo fertility-preserving hormonal-based therapy for endometrial cancer respond to progesterone-based therapy. Data on fertility-sparing methods with grade 1 endometrial cancer show excellent response rates ranging from 55 % to 100 % (Table 3). This table summarizes the larger and/or prospective studies published for treatment of low-grade endometrial cancer. Response rates are favorable; however, recurrence rates range from 0 % to 57 %. Additionally, there have been two published meta-

Table 3 Selected reports of conservative management for endometrial carcinoma

Author	Number of patients	Therapy	Duration	Regression n/N (%)	Progression n/N (%)	Relapse n/N (%)	Surveillance	Complications
Ushijima, 2007	22	MPA 600 mg + ASA 81 mg then cyclic estrogen/progesterone	26 weeks then 6 months	12/22 (55)	0/22 (0)	8/14 (57)	TVUS and EMB at 8 and 16 weeks Hysteroscopy D&C at 26 weeks	Weight gain, liver dysfunction, abnormal coagulation factors
Park, 2013a	148	MPA 500 mg or MA 160 mg	Mean 8 months	115/148 (78)	0/148 (0)	35/115 (30)	Exam, US/MRI every 3–6 months	Not reported
Minig, 2011	14	LNG-IUD × 1y + GnRH analog × 6 m	1.5 years	8/14 (57)	4/14 (29)	2/14 (14)	TVUS and D&C or EMB at 6 months and 1 year	None
Pronin, 2015	32	LNG-IUD + goserelin monthly	Minimum 6 months	23/32 (72)	0/32 (0)	2/32 (6)	TVUS at 3 and 6 months, EMB at 3 months then TVUS/MRI and hysteroscopy D&C every 6 months	Not reported
Shan, 2013	26	D&C then MA 160 mg – increased dose for progression or no response	>/= 12 weeks	21/26 (81)	0/26 (0)	6/21 (29)	TVUS monthly until CR then every 3 months. D&C or EMB every 6 months	Weight gain, elevated GGT
Mazzon, 2010	6	Hysteroscopic resection followed by MA 160 mg	6 months	6/6 (100)	0/6 (0)	0/6 (0)	TVUS and D&C hysteroscopy every 3 months × 1 year then 6 months × 2 years	None

analyses on conservative treatments for endometrial cancer. The earlier reported on 32 studies published between 1985 and 2011, and reported a 76 % regression rate (defined as no residual cancer or complex atypical hyperplasia). The recurrence rate was 40.6 %, and median follow-up period ranged from 11 to 76 months (Gallos et al. 2012). Another contemporary meta-analysis published in 2012 on 38 studies from 2004 to 2011 reported an initial response rate of 74 %. Overall however, 48.2 % achieved a durable complete response and 35.4 % experienced a recurrence; the median follow-up time ranged from 0 to 30 years (Gunderson et al. 2014). There has been no head-to-head trial comparing the efficacy of MPA versus MA, and overall response rates seem similar. One should note that the doses of MPA for treatment of endometrial cancer are typically high, unlike the low doses (10 mg) that are frequently administered for management of benign gynecologic conditions.

There is less information specifically regarding outcomes for potentially higher risk cases, which include grade 2 or 3 histology and those with myometrial invasion. Due to the understanding that more aggressive histologies have lower response rates, very few researchers have studied conservative management in women with grade 2 or 3 endometrial cancer or with myometrial invasion. In a more recent review article, Park (2015) summarized the available data on fertility-sparing management of grade 2–3 endometrial cancer or patients with myometrial invasion. The combined total included only 61 patients, with most studies reporting on only 1–3 patients. Response rates ranged from 0 % to 100 % (keeping in mind the sample size of 1–3). The largest series was reported by Park et al. (2013b) which included stage IA endometrial cancer of all histologic grades and some with myometrial invasion, treated with oral progestins. Overall, 77 % (37/48) achieved complete response. Women with grade 2–3 histology and no myometrial invasion had a response rate of 76 % (13/17), and recurrence rate of 23 % (3/13), whereas those with grade 2–3 with superficial myometrial invasion had a complete response of 87 % (7/8); however, recurrence rate was 71 % (5/7). Those with stage IA, grade 1 with superficial myometrial invasion had a complete response of 73 % (17/23) and recurrence rate of 47 % (8/17) (Park et al. 2013a). Once a patient has achieved a complete response, the primary recommendation is for immediate attempt at pregnancy. If pregnancy is not desired or will be delayed, maintenance therapy is suggested via either oral progestin or LNG-IUD.

6 Risk of Recurrence

While many studies cited here report encouraging data on durable response to conservative management, lifetime remission is never a guarantee. According to Gallos et al., the recurrence rate for conservatively managed endometrial cancer in their large meta-analysis was 40.6 % (Gallos et al. 2012). Conversely, in the comparison study of MA versus MPA, Park et al. showed a 55 % durable response. Recurrence in this study was significantly associated with BMI >25. Protective factors included treatment with MPA, maintenance therapy after complete response, and pregnancy (Park et al. 2013a). Park et al. also examined the recurrence rates for women receiving infertility treatment compared to those who conceived without assistance and found no significant difference ($P = 0.335$). Again, pregnancy appeared to be protective as 76 % of women who conceived were disease free at 5-year follow-up versus 62 % of women who did not conceive (Park et al. 2013d). Ichinose et al. report similar findings in a smaller cohort of women who had achieved complete response: 19 % recurrence in the group achieving live birth versus 70 % recurrence in the nulliparous group (Ichinose et al. 2013). In women with grade 2–3 disease or myometrial invasion, recurrence rises to 23–71 % in Park's study, and the highest relapse rate was seen in the patients with evidence of myometrial invasion. On multivariate analysis, however, the group found that myometrial invasion itself was not an independent predictor of treatment failure (Park et al. 2013b).

Retreatment with oral progestins for recurrence after initial complete response continues to be studied. Park et al. have shown high complete (re)response rates with both MA and MPA

(85 %) as well as 85 % durable complete response (Park et al. 2013c).

7 Fertility Outcomes

Pregnancy data after conservative management of endometrial cancer is relatively reassuring. In general, women who have achieved a complete response from endometrial cancer should be counseled to promptly pursue fertility if desired, as the reported recurrence rates are relatively high and frequently base-line risk factors for development of endometrial cancer have not changed. Referral to a reproductive endocrinologist is reasonable as many of these patients likely have underlying clinical risk factors for decreased fertility (PCOS, anovulation). Conversely, some patients have been diagnosed with EC while undergoing evaluation for infertility. The data on the safety of assisted reproductive therapies in the setting of prior endometrial cancer are limited. Most of the concern relates to the use of high-dose estrogen-based ovarian stimulation protocols, though a few studies have reported their relative safety. If patients do not seek immediate fertility, one should consider use of some type of hormonal maintenance therapy (progesterone-based, LNG-IUD, or combination oral contraceptive).

Reported pregnancy rates range from 25 % to nearly 73 % (Minig et al. 2011; Park et al. 2013d; Shan et al. 2013). In a large meta-analysis including 559 women, the live birth rate was approximately 28 % (Gallos et al. 2012). Multiple studies have reported on nearly every form of assisted reproductive technology utilized by women achieving a complete response after conservative management. No studies have specifically compared the reported methods including ovulation induction with timed intercourse, hyperstimulation with intrauterine insemination, and in vitro fertilization.

The largest study to date by Park et al. followed 141 women who achieved remission with oral progestins. The overall live birth rate for the entire cohort was 26 %, though if considering only those who attempted pregnancy, 73 % conceived and 66 % resulted in live births. Of those attempting pregnancy, one third had no assistance with reproduction, while two thirds underwent infertility treatments. Patients receiving infertility therapies were more successful at conceiving (86 % vs. 50 %) though both groups reported on patients who achieved multiple pregnancies. There were almost twice as many multiples in the treatment group compared to no treatment (11 % vs. 6 %). Out of a total 52 live births, only 2 anomalies were noted: one child with polydactyly and another with club foot. Ectopic and spontaneous abortion rates were similar in each group and approached population incidence. The preterm delivery rate was higher in the infertility treatment group (8 % vs. 18 %); however, this is likely related to higher incidence of multiple gestation pregnancies (Park et al. 2013d).

8 Surveillance

Upon achievement of remission, or complete response to therapy, surveillance measures must be performed thereafter, in order to monitor for potential recurrence and/or metastases. The National Comprehensive Cancer Network (NCCN) recommends surveillance with history, physical exam, and endometrial sampling every 3–6 months via D&C or in-office endometrial biopsy. Some investigators also have recommended checking serial CA-125, and use of imaging such as transvaginal ultrasound, MRI, or CT scans. These are not universally recommended but may be considered particularly if symptoms of potential metastases arise (pain, gastrointestinal, or genitourinary irregularities). Park et al. recommend against hysteroscopic biopsy during the follow-up period for women planning to conceive. The prevailing notion underlying this recommendation is that repetitive surgical disruption of the endometrium could negatively impact the basal layer and increase risk of intrauterine adhesions (Park and Nam 2015).

9 Definitive Management

In his review on conservative management of endometrial cancer, Park writes: "Surveillance after successful progestin therapy should include periodic interviews to explore any symptoms, physical examinations, and transvaginal ultrasonography at 3-month intervals. However, periodic pathologic evaluations of the endometrium, using office endometrial biopsy, D&C, or hysteroscopy, need not be recommenced in patients who do not have symptoms or signs of recurrence"(Park and Nam 2015). The caveat to this recommendation is that once childbearing is complete, even in the absence of verified recurrence, hysterectomy should be performed. While some studies recommend hysterectomy if no response by 6–9 months, management and retreatment for up to 12 months without adverse effect has been reported (Park and Nam 2015).

While the discussion around ovarian preservation at the time of hysterectomy has been somewhat fraught, it appears this is a safe option especially in younger populations who stand to benefit from endogenous estrogens in their premenopausal years. Some studies have reported relatively high rates (19–25 %) of concurrent ovarian malignancy in young patients undergoing hysterectomy and BSO for endometrial cancer (Soliman et al. 2005; Walsh et al. 2005). However, in a study of over 3000 women with endometrial cancer, 400 had ovarian preservation. In this large study, ovarian preservation had no effect on either cancer-specific or overall survival suggesting that ovarian preservation is safe (Wright et al. 2009).

10 Medically Inoperable Patients

Medically inoperable patients fall into two groups: low-grade/early stage whose medical comorbidities preclude surgical management, and advanced stage cases with diffuse metastatic disease that is considered unresectable. Data gathered in younger populations desiring fertility can be extrapolated to women with severe comorbidities who have low-grade endometrial cancers and provide good support for this option. A 2004 GOG study using MPA and Tamoxifen to treat advanced or recurrent endometrial cancer showed 33 % response rate lending support to combinations of oral regimens (Whitney et al. 2004). The LNG-IUD has been more recently studied in populations whose multiple comorbidities prevent surgical management of endometrial cancer. Dhar et al. employed the IUD alone, while Montz et al. performed D&C with insertion of IUD. In each of these studies, complete response was observed in less than half of the study population (Dhar et al. 2005; Montz et al. 2002). Given favorable side effect profiles, progestins or the LNG-IUD may be preferable for early stage patients. Primary radiation and chemotherapy for medically inoperable patients are alternative methods which, though effective, carry high rates of side effects and toxicities. In a consensus statement from the American Brachytherapy Society, Schwarz et al. recommend dosing uterus, cervix, and upper 1–2 cm of vagina with brachytherapy and combining this treatment with external beam radiation (Schwarz et al. 2015). The Society of Gynecologic Oncology makes a Level A recommendation for chemotherapy in advanced endometrial cancer of any cell type. Moreover, chemotherapy in combination with radiotherapy provides improved response over either modality alone (Burke et al. 2014a). Finally, in a recent study conducted by Slomovitz et al., patients who had failed $\geq$2 chemotherapy regimens were treated with an mTOR inhibitor and aromatase inhibitor combination. The study population achieved 40 % complete response with low toxicity (Slomovitz et al. 2015).

11 Conclusion

Conservative management of endometrial cancer, particularly in women with low-grade, early stage disease is a timely issue that is becoming more prominent with the rising obesity epidemic. There is increasing evidence in support of therapies that are largely hormone based; however, patients must be counseled in detail regarding the potential risk for cancer recurrence and that definitive

treatment with hysterectomy is still recommended when feasible. With careful patient selection and adequate surveillance, fertility can be preserved for many young endometrial cancer patients, and those who achieve response are likely to be able to conceive and bear children. Conservative therapy may also be a very reasonable option for patients with severe comorbidities who are deemed nonsurgical candidates. Future studies may identify additional therapies in addition to progesterone-based agents for the conservative treatment of endometrial cancer

12 Cross-References

- Benign and Malignant Pathology of the Endometrium
- Diagnosis and Management of the Cancer of the Uterus
- Endometrial Hyperplasia
- Impact of Obesity on Gynecological Diseases
- Workup and Management of Polycystic Ovary Syndrome

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Management of Metastatic and Recurrent Cervical Cancer

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Abstract

Treatment guidelines for uterine cervical cancer have been established based on the findings of randomized clinical trials conducted in the past few decades. Although most cases of cervical cancer can be adequately managed with standard treatments, problems can arise in cases involving unusual presentations. Metastatic and recurrent cervical cancers are considered to be incurable. Although attempts have been made to treat patients with metastatic or recurrent cervical cancer with a variety of approaches including chemotherapy, radiotherapy, and surgery (as monotherapies or in combination), such patients have a dismal prognosis, with a reported 5-year survival rate of <10 %. In this chapter, we first review the current management strategies for metastatic or recurrent cervical cancer. Then, we review the management strategies for unusual cases of cervical cancer, such as those involving the incidental detection of cervical cancer during pregnancy or in hysterectomy specimens, bulky lymph nodes, cervical stump cancer, cervical bleeding or ureteral obstruction, or unusual cervical cancer cell types.

Keywords

Metastatic cervical cancer • Recurrent cervical cancer • Chemotherapy • Cervical cancer in pregnancy • Unusual histology

1 Introduction

Although most cases of cervical cancer can be adequately managed with standard treatments, problems can arise in cases involving unusual presentations. In this chapter, we summarize the management strategies for such unusual conditions, including metastatic and recurrent cervical cancer, and cases of cervical cancer involving the incidental detection of the disease during pregnancy or in hysterectomy specimens, bulky lymph nodes, cervical stump cancer, cervical bleeding or ureteral obstruction, or unusual cancer cell types.

2 Stage IVB Cervical Cancer

Roughly 10 % of newly diagnosed cervical cancer patients have distant metastases at the time of the initial diagnosis and, thus, are diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IVB disease (SEER Stat Fact Sheets: Cervix Uteri Cancer). These patients represent a heterogeneous population, ranging from patients with nodal metastases to those with metastases to the visceral organs.

Due to the heterogeneity of such patients' symptoms at presentation, the optimal treatment varies according to the patient's symptoms, performance status, and disease characteristics.

Although no particular treatment has been demonstrated to be superior, a variety of therapeutic options are currently available for stage IVB cervical cancer: Platinum-based combination chemotherapy is recommended for patients with organ metastasis who are not candidates for definitive radiotherapy or exenterative surgery with the aim of achieving locoregional control (Monk et al. 2009; Tewari et al. 2014; Varia et al. 1998). To date, stage IVB and recurrent cervical cancer have been treated with the same chemotherapy regimens. Patients with limited distant nodal metastasis, such as metastasis to the para-aortic lymph nodes (PALN) or supraclavicular lymph nodes, might be candidates for radiotherapy with curative intent involving an extended radiation field (Grigsby et al. 1998; Monk et al. 2009; Tewari et al. 2014; Varia et al. 1998). Patients with poor performance statuses are usually treated with palliative treatment alone. However, these treatments only achieve limited improvements in survival, resulting in a 5-year survival rate of 10–20 % (Monk et al. 2009; Tewari et al. 2014; Yoon et al. 2015).

3 Recurrent Cervical Cancer

3.1 Diagnosis

It is estimated that approximately 35 % of patients with invasive cervical cancer will develop recurrent or persistent disease after the primary

treatment, and recurrent cervical cancer patients have a dismal prognosis, with a reported 1-year survival rate of roughly 20 %.

The diagnosis of recurrent cervical cancer is often difficult. The cytological evaluation of irradiated cervix tissue is particularly difficult because of the distortion produced in the exfoliated cells. Thus, the diagnosis of recurrent cervical cancer should be confirmed histologically whenever possible to avoid misdiagnosis and unnecessary treatment.

3.2 Treatment

The treatment of recurrent cervical cancer depends on the mode of the primary treatment and the site of recurrence. Single distant recurrent lesions, such as isolated recurrent lung or PALN lesions, are usually treated with surgery or radiotherapy. Patients that suffer recurrence in the central pelvis after primary surgery can be salvaged with radiotherapy. On the other hand, patients that develop central pelvic recurrence after primary radiotherapy can be treated with curative pelvic surgery (either pelvic exenteration (PE) or radical hysterectomy (RH)). Patients with pelvic sidewall disease or multiple recurrent lesions are usually treated with platinum-based chemotherapy.

3.2.1 Chemotherapy

A large proportion of patients with recurrent disease develop tumors in a previously irradiated area. As the irradiated field is usually fibrotic and avascular, it is difficult to obtain high blood flow and achieve the optimal tissue concentration of the administered anticancer agent. Moreover, as ureteral obstruction is common in patients with recurrent cervical cancer, platinum-based chemotherapy is sometimes avoided.

The findings of phase III trials that were conducted to establish the optimal chemotherapy regimen for uterine cervical cancer are summarized in Table 1 (Leath and Straughn 2013).

A previous study by the Gynecologic Oncology Group (GOG) showed that the i.v. administration of 50 mg/m^2 cisplatin every 3 weeks as a single agent is superior to all other single-agent options (GOG 43). Subsequent phase III trials have demonstrated that cisplatin-based doublet chemotherapies are superior to single-agent cisplatin. In a phase III study comparing four cisplatin-based doublet chemotherapies (cisplatin + paclitaxel, cisplatin + topotecan, cisplatin + gemcitabine, and cisplatin + vinorelbine), cisplatin + paclitaxel produced the longest progression-free survival (PFS) and overall survival (OS) periods, although the differences were not statistically significant (GOG 204). Based on these results, cisplatin + paclitaxel became the standard chemotherapy for patients with recurrent cervical cancer. Subsequently, in an effort to mitigate the nephrotoxicity encountered during the use of cisplatin and shorten the chemotherapy infusion interval in order to allow cisplatin + paclitaxel chemotherapy to be administered on an outpatient basis, the Japanese Clinical Oncology Group (JCOG) performed a prospective, non-inferiority, phase III trial comparing cisplatin + paclitaxel with carboplatin + paclitaxel. In the survival analysis, carboplatin + paclitaxel was not found to be inferior to cisplatin + paclitaxel. As anticipated, the cisplatin-containing regimen exhibited greater renal toxicity, while the carboplatin-containing regimen produced greater thrombocytopenia (JCOG 0505).

A recent randomized trial found that combining bevacizumab with cisplatin + paclitaxel or paclitaxel + topotecan was superior to either combination alone (GOG 240). In this study, although 75 % of the enrolled patients had previously received platinum-based agents, the topotecan + paclitaxel arm was not demonstrated to be superior or inferior to the cisplatin + paclitaxel arm (hazard ratio: 1.20; 95 % confidence interval: 0.82–1.76), indicating that non-platinum-based chemotherapy doublets are not more effective than cisplatin + paclitaxel in this patient population. Even when bevacizumab was used in combination with cisplatin + paclitaxel, it still only resulted in a median OS time of 17 months (Tewari et al. 2014). Accordingly, cost, convenience, and patient preference should be taken into consideration before offering this regimen to patients.

Table 1 Summary of phase III trials of chemotherapy for recurrent or advanced cervical cancer

Trial	Arms	Response rates (%)	PFS (months)	OS (months)	Comments
GOG 43	Arm 1: Cisplatin 50 mg/m^2/3 weeks Arm 2: Cisplatin 100 mg/m^2/3 weeks Arm 3: Cisplatin 20 mg/m^2×5 days/3 weeks	Arm 1: 20.7 Arm 2: 31.4 Arm 3: 25.0	Arm 1: 3.7 Arm 2: 4.6 Arm 3: 3.9	Arm 1: 7.1 Arm 2: 7.0 Arm 3: 6.1	Cisplatin 50 mg/m^2/3 weeks became standard
GOG 110	Arm 1: Cisplatin Arm 2: Cisplatin + Ifosfamide	Arm 1: 17.8 Arm 2: 31.1	Arm 1: 3.2 Arm 2: 4.6 *	Arm 1: 8.0 Arm 2: 8.3	*PFS was improved (p=0.003)
GOG 149	Arm 1: Cisplatin + Ifosfamide Arm 2: Cisplatin + Ifosfamide + Bleomycin	Arm 1: 32 Arm 2: 31.2	Arm 1: 4.5 Arm 2: 5.1	Arm 1: 8.5 Arm 2: 8.4	
GOG 169	Arm 1: Cisplatin Arm 2: Cisplatin + Paclitaxel	Arm 1: 19 Arm 2: 36	Arm 1: 2.8 Arm 2: 4.8 *	Arm 1: 8.8 Arm 2: 9.7	*PFS was improved (p<0.001)
GOG 179	Arm 1: Cisplatin Arm 2: Cisplatin + Topotecan	Arm 1: 13 Arm 2: 26.7	Arm 1: 2.9 Arm 2: 4.6*	Arm 1: 6.5 Arm 2: 9.4 *	*Both PFS (p=0.014) and OS (p=0.017) were improved
GOG 204	Arm 1: Cisplatin + Paclitaxel Arm 2: Cisplatin + Topotecan Arm 3: Cisplatin + Gemcitabine Arm 4: Cisplatin + Vinorelbine	Arm 1: 29.1 Arm 2: 23.4 Arm 3: 22.3 Arm 4: 25.9	Arm 1: 5.8 Arm 2: 4.6 Arm 3: 4.7 Arm 4: 4.0	Arm 1: 12.9 Arm 2: 10.3 Arm 3: 10.3 Arm 4: 10.0	No significant differences were observed Cisplatin + Paclitaxel became standard
JGOG0505	Arm 1: Cisplatin + Paclitaxel Arm 2: Carboplatin + Paclitaxel	Arm 1: 58.8 Arm 2: 62.6	Arm 1: 6.9 Arm 2: 6.2	Arm 1: 18.3 Arm 2: 17.5	Non-inferiority of carboplatin + paclitaxel was demonstrated
GOG240	Arm 1: Cisplatin + Paclitaxel Arm 2: Cisplatin + Paclitaxel + Bevacizumab Arm 3: Topotecan + Paclitaxel Arm 4: Topotecan + Paclitaxel + Bevacizumab	Arm 1: 45 Arm 2: 50 Arm 3: 27 Arm 4: 47	Arm 1 + 3: 5.9 Arm 2 + 4: 8.2 * Arm 1 + 2: 7.6 Arm 3 + 4: 5.7	Arm 1: 14.3 Arm 2: 17.5 ** Arm 3: 12.7 Arm 4: 16.2 Arm 1 + 3: 13.3 Arm 2 + 4: 17 *** Arm 1 + 2: 15 Arm 3 + 4: 12.5	Addition of bevacizumab improved PFS and OS *Arm 1 + 3 versus Arm 2 + 4: p = 0.0002 **Arm 1 versus Arm 2: p = 0.04 ***Arm 1 + 3 versus Arm 2 + 4: p = 0.003

Table 2 Recent larger series of pelvic exenteration for cervical cancer

First author	*N*	Severe morbidity (%)	Operative mortality (%)	5-year survival (%)
Chiantera 2014	167	34,7	6	38
Yoo 2012	61	44	0	56
Schmidt 2012	212	51	5	41
Marnitz 2006	35	38	5.5	27
Goldberg 2006	103	25	1	48
Berek 2005	67	23	4.4	54

3.2.2 Surgical Treatments

Pelvic Exenteration

PE is a radical surgical procedure involving the en bloc resection of the pelvic organs, including the internal reproductive organs, the distal urinary tract (bilateral ureters, bladder, and urethra), and the anorectum. This procedure was first described by Alexander Brunschwig in 1948 (Brunschwig 1948). PE is a potentially curative option for selected patients with recurrent or persistent cervical cancer and results in a reported 5-year survival rate of 30–50 % (Berek et al. 2005; Chiantera et al. 2014; Goldberg et al. 2006; Marnitz et al. 2006; Schmidt et al. 2012; Yoo et al. 2012). Major morbidities occur in 20–40 % of cases and are mainly related to the urinary and digestive diversion procedures and the associated reconstructive surgery. Global mortality varies from 0 % to 10 %, depending on the study (Table 2).

Radical Hysterectomy

Selected patients that exhibit limited recurrent disease in the uterine cervix after primary radiotherapy might be suitable for RH. Although this procedure is associated with a high morbidity rate, it can cure patients without the need for urinary and digestive diversion. According to a previous report, this procedure results in a 5-year survival rate of 49 %, but major morbidities occur in 44 % of cases (Maneo et al. 1999).

Radiotherapy

Recurrence outside of the irradiated field can be successfully treated with irradiation with or without concurrent chemotherapy. However, the utility of re-irradiation for pelvic recurrence, which might be an option for a selected group of patients, is disputed. Although re-irradiation is associated with little or no treatment-related mortality and preserves the structures and functions of the pelvic organs, it is often avoided due to concerns regarding severe late toxicities, such as fistula formation. Recent reports about re-irradiation involving interstitial brachytherapy alone have shown cure rates ranging from 20 % to 50 % and grade 3/4 late complication rates ranging from 10 % to 40 %. None of the patients in these studies died (Badakh and Grover 2009; Charra et al. 1998; Mabuchi et al. 2014; Prempree et al. 1979; Randall et al. 1993).

4 Invasive Cancer that is Detected After Simple Hysterectomy

In cases of invasive cancer that are found after simple hysterectomy, the treatment options include pelvic external beam radiotherapy or surgery consisting of radical parametrectomy, upper vaginectomy, and pelvic lymphadenectomy. It is generally more difficult to perform a reoperation than an RH, as the bladder and rectum firmly adhere to the vaginal vault and can also adhere to each other. In a previous study by Ayhan et al., operative complications occurred in 5 out of 27 patients (18.5 %) (bladder perforation, intestinal perforation, ureteral injury, and external iliac vein injury), and the OS rate was 88.9 % (Ayhan et al. 2006). In a case series in which postoperative radiotherapy was employed, Hopkins et al. reported that radiation therapy in the immediate postoperative period produced a survival of 88 %, compared to observation only with a 69 % survival ($P = 0.10$) (Hopkins et al. 1990).

5 Cancer of the Cervical Stump

In cases in which invasive cancer develops in a cervical stump, the treatment principles are the same as those employed for patients whose uteruses remain intact. When surgery is performed as an initial treatment, the bladder sometimes adheres firmly to the stump; therefore, dissection should be performed carefully. When radiotherapy is considered as an initial treatment, we have to recognize (1) that the ability to deliver an adequate dose of radiation to the primary tumor depends on the length of the cervical canal and (2) that it is difficult to accomplish this if the canal is less than 2 cm in length. Hellström et al. reported in their case–control study that the 5-year survival rate of patients with cervical stump cancer was similar to that observed in patients with intact uteruses (Hellström et al. 2001).

6 Cervical Bleeding

Cervical bleeding sometimes occurs after pelvic examinations or biopsies. When the bleeding cannot be controlled with gauze packing, embolization of the hypogastric or uterine arteries should be considered. However, there is a concern that such arterial embolization might increase tumor hypoxia and decrease the sensitivity of cervical cancer to radiotherapy.

7 Invasive Cervical Cancer with Bulky Lymph Nodes

Enlarged lymph nodes (>2 cm diameter) should be removed through an extraperitoneal approach before the initiation of radiotherapy, as they cannot be cured by external beam radiotherapy. Cosin et al. reported that the resecting of enlarged lymph nodes can improve a patient's prognosis so that it is similar to those of patients with micrometastasis without increasing the treatment-related morbidity or mortality rate (Cosin et al. 1998).

8 Ureteral Obstruction

Ureteral obstruction due to cervical cancer is an ominous sign and can occur due to compression by the primary or metastatic tumor, retroperitoneal adenopathy, or direct tumor invasion. Previous studies have indicated that hydronephrosis is an independent poor prognostic indicator in patients with advanced cervical cancer (Pradhan et al. 2011; Rose et al. 2010). Moreover, acute ureteral obstruction associated with renal failure, pain, or fever is an emergency that requires prompt evaluation and treatment. The current management options for this condition involve decompression by a cystoscopically inserted ureteral stent or a percutaneous nephrostomy tube. Generally, patients that are treated with stents experience significantly more urinary symptoms and require more assistance with nephrostomy care.

9 Cervical Cancer in Pregnancy

9.1 Incidence

Cervical cancer is the most commonly diagnosed gynecological malignancy during pregnancy. The incidence rate of the condition varies from 0.1 to 12 per 10,000 pregnancies (Al-Halal et al. 2013; Duggan et al. 1993; Takushi et al. 2002).

9.2 Symptoms

Although vaginal bleeding is the main symptom seen in pregnant patients with cervical cancer, abnormal bleeding is often mistakenly attributed to pregnancy-related complications. Pelvic pain and bowel or urinary symptoms can also be mistakenly linked to pregnancy-related complications. Thus, the diagnosis of cervical cancer is sometimes delayed, especially in cases in which cervical cancer is not initially suspected.

9.3 Diagnosis

In pregnant women, the diagnosis of cervical cancer should be based on colposcopy-directed punch biopsies, which can be performed safely during pregnancy. Endocervical curettage is contraindicated during pregnancy. Cone biopsies should be performed sparingly, as they are associated with hemorrhaging, abortion, and premature labor. In strictly indicated cases involving a strong suspicion of invasive disease, the optimal time to perform a conization during pregnancy is between 14 and 20 weeks' gestation.

9.4 Distribution by Stage

As pregnancy is associated with frequent obstetric examinations, most patients that are diagnosed with cervical cancer during pregnancy present with early-stage disease (Zemlickis et al. 1991).

9.5 Staging

The general rule when performing radiological and nuclear medicine examinations during pregnancy is that the radiation dose should be kept as low as possible and that such examinations should be avoided when possible. Thus, pelvic computed tomography (CT) and fluorodeoxyglucose positron emission tomography/CT are usually avoided. Magnetic resonance imaging (MRI) can be used safely during pregnancy to evaluate tumor size, stromal invasion, vaginal and parametrial invasion, and lymph node infiltration (Kanal et al. 2007). At present, there are no known deleterious effects of exposing a developing fetus to MRI.

9.6 Management

Decisions regarding the management strategy should be made after full discussions with both of the fetus' parents regarding the risks to both mother and fetus.

In cases in which pregnancy preservation is not included in the treatment aims, cervical cancer can be managed using a similar approach to that adopted for nonpregnant women. RH and pelvic lymphadenectomy can be performed during any trimester, either with the fetus in situ or after a classic cesarean section. In cases in which definitive radiotherapy is employed as a primary treatment, spontaneous abortion usually occurs after external beam radiotherapy. If it does not occur, hysterotomy and evacuation of the uterus should be performed before the initiation of intracavitary brachytherapy.

If pregnancy preservation is desired, the treatment choice is influenced by the gestational age of the fetus and the patient's disease stage. The mother must be informed and must understand that pregnancy-preserving management strategies for invasive cervical cancer remain experimental.

For patients that are diagnosed with cervical cancer before 20 weeks' gestation, pregnancy interruption and immediate treatment are usually recommended. However, in cases of stage IA1 disease that are diagnosed after conization and exhibit clear negative margins, it is reasonable to allow the pregnancy to proceed until term. Diagnostic conization should be performed at 12–20 weeks' gestation. A vaginal delivery should be chosen unless obstetric indications for cesarean section are present.

For patients that are diagnosed after 24 weeks' gestation, a watch and wait strategy should be employed until the fetus is viable. However, when progressive disease is observed before fetal maturity, early delivery or neoadjuvant chemotherapy (NACT) is advocated.

A dilemma arises when patients are diagnosed with cervical cancer between 20 and 24 weeks' gestation. Due to the limited number of such cases, it is impossible to offer a precise risk estimate for individual patients. In patients with stage IA2 or higher stage tumors, pelvic lymphadenectomy can be used to identify node-positive high-risk patients in whom it is necessary to terminate the pregnancy, although the therapeutic value of pelvic lymphadenectomy is unclear. A

recent literature review reported that recurrence did not occur in pregnant women with stage IB1 tumors without lymph node metastasis (Morice et al. 2012; Zagouri et al. 2013). In those with stage IB2 and higher-stage tumors, NACT is the only way to prevent disease progression while allowing time for the fetus to achieve viability.

It has been reported that during pregnancy, NACT involving a platinum-based agent in combination with paclitaxel is superior to NACT involving a single platinum-based agent in terms of response rate (Amant et al. 2014). Thus, NACT involving paclitaxel (175 mg/m^2) in combination with cisplatin (75 mg/m^2) or carboplatin (AUC of 5–6) every 3 weeks is the currently recommended regimen.

Although several cases in which the patient was treated with pregnancy-preserving radical trachelectomy have been reported, in the absence of obstetric safety data, this procedure cannot be recommended at this time.

9.7 Prognosis

Previous studies have shown that pregnant and nonpregnant cervical cancer patients exhibit identical survival rates (Zemlickis et al. 1991). The favorable overall prognosis of pregnant patients with cervical cancer seems to be due to the greater proportion of pregnant patients that present with stage I disease.

10 Unusual Histological Types

10.1 Glassy Cell Carcinoma

Glassy cell carcinoma was first described in 1956. The latter study reported that the neoplastic cells found in glassy cell carcinoma exhibit the following features: a moderate amount of cytoplasm with a ground-glass appearance, distinct cell walls, and large nuclei with prominent nucleoli (Cherry and Glucksmann 1956). Glassy cell carcinoma is now regarded as a poorly differentiated form of mixed adenosquamous carcinoma. Previous studies have suggested that glassy cell carcinoma is associated with a high risk of distant failure and a worse prognosis than squamous cell carcinoma (Guitarte et al. 2014). However, due to the rarity of the disease and the lack of prospective studies examining it, no specific management strategy for glassy cell carcinoma has been developed. Thus, it is usually treated according to the management strategy for squamous cell carcinoma.

10.2 Small Cell Carcinoma

Small cell carcinoma is most frequently found in the lungs, with pulmonary small cell carcinoma accounting for 95 % of all cases of the condition (van Meerbeeck et al. 2011). Small cell carcinoma of the uterine cervix is a rare histological entity, representing roughly 1 % of cases of invasive cervical cancer (Satoh et al. 2014). Histologically, roughly one-third of small cell carcinomas are positive for the neuroendocrine markers chromogranin, synaptophysin, and CD56, whereas the remaining lesions only express epithelial markers, such as cytokeratin. Previous studies have suggested that small cell carcinoma is associated with higher incidences of lymphovascular space invasion, lymph node metastasis, and distant metastasis, even in the early stages of the disease, a higher rate of recurrence, and decreased survival compared with squamous cell carcinoma and adenocarcinoma (Chen et al. 2008; Kim et al. 2009; McCusker et al. 2003). Due to the rarity of this disease and the lack of a prospective study examining it, no specific management strategy for small cell carcinoma has been established. Currently, early-stage small cell carcinoma is generally treated with surgery, and advanced disease is treated with concurrent chemoradiotherapy. However, previous retrospective studies have suggested that postoperative adjuvant therapy either with radiotherapy or chemotherapy did not improve the prognosis of patients with cervical small cell carcinoma (Cohen et al. 2010; Lee et al. 2008; Tian et al. 2012). In contrast, recent retrospective studies have indicated that the administration of adjuvant chemotherapy after RH or definitive

radiotherapy is effective against the condition (Kuji et al. 2013; Wang et al. 2012). Etoposide and cisplatin were the most frequently used regimen in these trials. Given the propensity for early systemic spread and the high probability of distant treatment failure, the efficacy of adjuvant chemotherapy for cervical small cell carcinoma should be investigated in a prospective study (Kuji et al. 2013).

10.3 Sarcoma

Cervical sarcomas are rare tumors that constitute <1 % of all cervical malignancies. The seven most common types of cervical sarcoma are embryonal rhabdomyosarcoma, leiomyosarcoma, undifferentiated endocervical sarcoma, alveolar soft part sarcoma, Ewing's sarcoma, primitive neuroectodermal tumor, and liposarcoma (Fadare et al. 2006). As the previously reported cases were treated using a wide variety of treatments and involved small numbers of patients as well as patients that presented with different disease stages, the assessment of the natural history and intrinsic biological behavior of cervical sarcoma remains difficult. International collaborative investigations need to be conducted to establish guidelines for the management of this condition.

10.4 Lymphoma

Primary lymphoma of the uterine cervix is an extremely rare disease. Approximately a quarter of malignant lymphomas arise in extranodal organs. The most common locations of extranodal lymphoma are the gastrointestinal tract and skin, and about 1.5 % of extranodal lymphomas originate in the female genital tract, with the ovaries being the most commonly affected site (Upanal and Enjeti 2011).

Vaginal bleeding is the most common symptom at presentation. The Papanicolaou smear test is not useful for diagnosing uterine lymphoma. Instead, patients should be diagnosed based on histological and immunophenotypic evaluations of their biopsy samples. Histologically, B-cell lymphomas constitute the vast majority of uterine lymphomas, with the most frequent type being the diffuse large cell type (56 %) followed by follicular lymphoma (15 %).

Due to the rarity of uterine/cervical lymphoma, no standard treatment for primary uterine lymphoma has been established. In a recent review of 75 cases of malignant lymphoma (Upanal and Enjeti 2011), various treatment modalities were employed: surgery alone (25 %); surgery and chemotherapy (25 %); chemotherapy and radiotherapy (19 %); chemotherapy alone (19 %); chemotherapy, radiotherapy, and surgery (8 %); and surgery combined with radiotherapy (3 %). However, it remains unclear which primary treatment is the most advantageous. To preserve the reproductive function of young patients, combination chemotherapy alone has been advocated as a primary treatment in previous reports (Szánthó et al. 2003). In general, the overall prognosis of primary uterine lymphoma appears to be excellent and is comparable with those of other nodal lymphomas. In a study of 10 patients with uterine non-Hodgkin's lymphoma, Vang et al. reported a very good 5-year survival rate of 83 % (Vang et al. 2000).

11 Conclusion

Although most cervical cancers can be adequately managed with standard treatments, problems can arise in cases involving unusual presentations. Due to the limited numbers of such patients, it is difficult to conduct randomized studies of their conditions. Further prospective, collaborative studies need to be conducted to establish standard evidence-based treatments for unusual types of cervical cancer.

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Fertility-Sparing Treatment for Early-Stage Cervical Cancer

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Abstract

Fertility preservation is of paramount importance for young women that are diagnosed with early-stage cervical cancer. Women with stage IA1 disease can be treated with conization. Radical trachelectomy has been developed as a surgical method for preserving reproductive function, and the radical trachelectomy procedure has evolved significantly over the last 25 years. The candidates for radical trachelectomy include women of reproductive age with early-stage disease (stage IA2 or IB1) who do not possess any risk factors for recurrence (i.e., a lesion size of >2 cm or lymph node metastasis). Lymphovascular space invasion within the tumor is a risk factor for lymph node recurrence, but is not a contraindication for fertility-sparing surgery in cases in which it is the only risk factor present. Recently, neoadjuvant chemotherapy followed by fertility-preserving surgery has been proposed as an option for patients with larger lesions. Pregnancy after radical trachelectomy is associated with an increased risk of obstetric complications, including preterm delivery, infection, and preterm premature rupture of membranes. However, there are no effective interventions for preventing these complications.

Keywords

Cervical cancer • Fertility-preserving surgery • Trachelectomy

1 Introduction

In the United States, 46 % of uterine cervical cancers are diagnosed in women below the age of 44 (National Cancer Institute: Browse the SEER Cancer Statistics Review (CSR) 1975–2010). Thus, information regarding fertility-sparing options is an important part of pretreatment counseling, especially for women of childbearing age that are diagnosed at an early stage. The fertility-sparing options for such patients include conization and radical trachelectomy. Observational studies have suggested that these procedures result in good oncological and obstetric outcomes in carefully selected patients with early-stage cervical cancer.

2 Patients

2.1 Stage IA1 Disease Without LVSI

A cohort study of stage IA1 squamous cell carcinoma of the uterine cervix that analyzed data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database showed that there was no difference between the 5-year survival rates of patients that were treated with conization and those that underwent hysterectomy (98 % vs. 99 %) (Wright et al. 2010). Thus, stage IA1 patients without lymphovascular space involvement (LVSI) are indicated for conization alone. In cases in which the margins of the excised cone are positive, repeated conization or trachelectomy is recommended. Clinicians have to recognize that the risk of preterm delivery is increased after conization if the depth of the excised cone is >10 mm (Kyrgiou et al. 2006).

2.2 Stage IA1 Disease with LVSI, Stage IA2 Disease, and Stage IB1 Disease

A previous report has shown that 8.2 % of stage IA1 patients with LVSI have lymph node metastasis, compared with 0.8 % of those without LVSI (Mota 2003). Thus, pelvic lymphadenectomy should be included in the fertility-sparing surgical options for stage IA1 patients with LVSI. Radical trachelectomy plus pelvic lymphadenectomy or conization plus pelvic lymphadenectomy is recommended for childbearing women with stage IA1 disease and LVSI, stage IA2 disease, or stage IB1 disease.

2.2.1 Radical Trachelectomy Plus Pelvic Lymphadenectomy

Regarding cases in which the patient wants to preserve their fertility, women with stage IA1 disease and LVSI, stage IA2 disease, or stage IB1 disease are indicated for radical trachelectomy plus pelvic lymphadenectomy. Radical trachelectomy can be performed either through a vaginal or abdominal approach and can also be carried out using laparoscopic or robotic methods.

The criteria for radical trachelectomy vary slightly among institutions, but remain essentially unchanged from the original set proposed by Roy et al. in 1998 (Table 1) (Roy and Plante 1998). Although previous studies have shown that a tumor size of >2 cm is associated with increased risk of recurrence after radical trachelectomy (Marchiole et al. 2007; Mathevet et al. 2003; Plante et al. 2011), tumors that measure >2 cm, are very exophytic, and exhibit minimal stromal invasion might also be considered for radical trachelectomy.

A previous study of radical trachelectomy for cervical cancer found that 28 % of cervical tumors

Table 1 Criteria of radical trachelectomy

1. A desire for fertility
2. Histologically proven invasive cervical cancer
3. Squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma, without high-risk histology (e.g., neuroendocrine carcinoma)
4. Stage IA1 with lymphovascular space invasion, stage IA2, or stage IB1
5. Tumor size ≤2 cm
6. Tumor limited to the cervix
7. No evidence of lymph node metastasis and distant metastasis

Table 2 Oncological outcomes according to surgical procedures

Surgery	Author	No. of surgeries	Follow-up	Recurrences	Deaths
	Year		Months	n (%)	n (%)
VRT	Burnett et al. 2003	21	31	2 (9.5)	0 (0)
	Mathevet et al. 2003	109	76	4 (3.7)	3 (2.8)
	Shepherd et al. 2006	123	45	5 (4.1)	4 (3.3)
	Hertel et al. 2006	108	29	4 (3.7)	2 (1.9)
	Marchiole et al. 2007	118	95	7 (5.9)	5 (4.2)
	Beiner et al. 2008	90	51	5 (5.5)	3 (3.3)
	Sonoda et al. 2008	43	21	1 (2.3)	0 (0)
	Plante et al. 2011	125	93	6 (4.8)	2 (1.6)
	Cao et al. 2013	71	34.4	7 (9.9)	2 (2.8)
	Total	765		41 (5.4)	21 (2.6)
ART	Ungár et al. 2005	30	47	0 (0)	0 (0)
	Abu-Rustum et al. 2008	22	12	0 (0)	0 (0)
	Pareja et al. 2008	15	32	0 (0)	0 (0)
	Nishio et al. 2009	61	27	6 (9.8)	NA[a]
	Cibula et al. 2009	17	21.2	1 (5.9)	0 (0)
	Yao et al. 2010	10	NA	0 (0)	0 (0)
	Saso et al. 2012	30	24	3 (10)	2 (6.7)
	Muraji et al. 2012	23	NA	0 (0)	0 (0)
	Wethington et al. 2012	93	32	4 (4.3)	0 (0)
	Cao et al. 2013	55	20.6	0 (0)	0 (0)
	Total	356		14 (3.9)	2 (0.7)[b]
VRH	Steed et al. 2004	71	17	4 (5.6)	NA
	Jackson et al. 2004	50	52	2 (4.0)	2 (4.0)
	Marchiole et al. 2007	139	113	9 (6.4)	7 (5.0)
	Beiner et al. 2008	90	58	1 (1.1)	1 (1.1)
	Total	350		16 (4.6)	10 (3.6)[c]
ARH	Roy et al. 1996	27	27	1 (3.7)	NA
	Steed et al. 2004	205	21	13 (6.3)	NA
	Jackson et al. 2004	50	49	2 (4.0)	2 (4.0)
	Malzoni et al. 2009	62	71.5	4 (6.5)	NA
	Zhang et al. 2014	90	12.5	0 (0)	0 (0)
	Total	434		20 (4.6)	2 (1.4)[d]

NA not available, *VRT* vaginal radical trachelectomy, *ART* abdominal radical trachelectomy, *VRH* vaginal radical hysterectomy, *ARH* abdominal radical hysterectomy

[a]Three of six patients were lost to follow-up as of the time of the review

[b]Estimated without the data of Nishio et al. 2009

[c]Estimated without the data of Steed et al. 2004

[d]Estimated with the data of Jackson et al. 2004 and Zhang et al. 2014

that are resected by radical trachelectomy exhibit LVSI and that LVSI is associated with an increased risk of recurrence (Beiner and Covens 2007). However, when LVSI is the only risk factor present, it is not an exclusion criterion for radical trachelectomy, as it does not justify adjuvant therapy (Beiner and Covens 2007; Plante et al. 2011).

2.2.2 Conization Plus Pelvic Lymphadenectomy

Radical trachelectomy plus pelvic lymphadenectomy is a safer approach for stage IA1–IA2 disease when LVSI is present; however, conization plus pelvic lymphadenectomy might also be a useful treatment option (Maneo et al. 2011).

3 Outcomes

3.1 Surgical Outcomes

Approximately 10 % of planned radical trachelectomy procedures have to be abandoned because of the presence of lymph node metastasis on frozen sections or positive endocervical margins (Tables 3 and 4). In a previous study, the mortality rate of patients who underwent vaginal radical trachelectomy (VRT) was 3.1 %, which was comparable with the 0–1.4 % observed in patients that were treated with abdominal radical hysterectomy (ARH) or abdominal radical trachelectomy (ART) (Averette et al. 1993).

3.2 Oncological Outcomes

A previous study suggested that the oncological outcomes of patients who undergo ART or VRT are similar to those of patients treated with ARH. As shown in Table 2, these procedures result in recurrence and death rates of approximately 5 % and 2 %, respectively. According to a recent review of VRT, recurrent lesions can develop predominantly in the parametrium or pelvis (Beiner and Covens 2007).

3.3 Prognostic Factors

The risk factors for recurrence have been intensively investigated, and tumors that measure >2 cm in diameter are consistently associated with an increased risk of recurrence. In addition, some studies have suggested that the presence of LVSI (Marchiole et al. 2007; Mathevet et al. 2003; Plante et al. 2011) and deep stromal invasion (DSI) of >10 mm (Diaz et al. 2008) are risk factors for recurrence; however, others have found that they are not associated with a higher risk of recurrence (Hertel et al. 2006; Plante et al. 2011). Although the prognostic significance of LVSI and DSI needs to be investigated further in larger studies, they are not considered to be contraindications for radical trachelectomy at this point. As neuroendocrine tumors are an aggressive subtype of cervical cancer and often recur rapidly, even if they have been completely removed and there is no lymph node or distant metastasis, radical trachelectomy cannot be recommended for women with this histological subtype of cervical cancer (Beiner and Covens 2007; Marchiole et al. 2007).

4 Surgical Procedures

The first successful trachelectomy procedure was performed via a vaginal approach by Dargent et al. in 1986, and the oncological and reproductive outcomes of patients who underwent VRT were presented at the Society of Gynecologic Oncologists meeting in 1994 (Ribeiro Cubal et al. 2012). A laparoscopic pelvic lymph node evaluation should be performed prior to VRT to rule out lymph node metastasis.

The abdominal approach was first reported by Smith et al. in 1997 (Ribeiro Cubal et al. 2012). The main advantages of ART are its greater radicality and feasibility compared with VRT.

Basically, the procedure for radical trachelectomy begins with the creation of paravesical and pararectal spaces and the dissection of the caudal bladder. Then, after the vesicouterine ligaments and cardinal ligaments have been divided, the cervix is removed. Finally, the uterine corpus and vaginal stump are reconstructed.

The endocervical margin of the specimen needs to be evaluated after the cervix has been removed to ensure that no residual disease remains. It is well known that the outcomes of post-conization pregnancies are influenced by the depth and size of the excised cervical tissue

Table 3 Reproductive outcomes for patients who underwent vaginal radical trachelectomy

Author (year)	No. of planned trachelectomies	Trachelectomy done	Fertility preserved	Attempting to conceive	Pregnant women	Pregnancies	Miscarriages		Deliveries		Patients pregnant at the time of report
							1st trimester	2nd trimester	At term	Preterm	
Schlaerth et al. 2003	12	10	10	NA	4	4	0	2	1	1	0
Burnett et al. 2003	21	19	18	NA	3	3	0	1	1	1	0
Mathevet et al. 2003	108	95	95	NA	33	56	14	8	29	5	0
Hertel et al. 2006	108	106	106	NA	18	18	3	0	4	8	3
Chen et al. 2008	16	16	16	NA	5	5	0	2	1	1	1
Sonoda et al. 2008	43	41	36	11	11	11	3	0	4	0	4
Pahisa et al. 2008	15	13	13	NA	3	3	0	0	1	0	2
Shepherd and Milliken 2008	158	158	138	NA	NA	88	19	12	19	25	7
Diaz et al. 2008	135	NA	118	NA	33	56	14	8	29	5	NA
Plante et al. 2011	140	125	122	NA	58	106	21	3	58	19	0
Dańska-Bidzińska et al. 2011	14	14	14	NA	2	2	1	0	1	0	0
Speiser et al. 2011	NA	212	212	76	50	60	5	3	27	18	4
Hauerberg et al. 2015	NA	120	108	72	55	77	16	2	20	33	3
Total number	770	929	1006	159	275	489	96	41	195	116	24

NA not available

Table 4 Reproductive outcomes for patients who underwent abdominal radical trachelectomy

Author (year)	No. of planned trachelectomies	Trachelectomy done	Fertility preserved	Attempting to conceive	Pregnant women	Pregnancies	Miscarriages		Deliveries		Patients pregnant at the time of report
							1st term	2nd term	At term	Preterm	
Ungár et al. 2005	33	30	NA	NA	3	3	1	0	2	0	0
Pareja et al. 2008	15	15	14	6	3	3	0	0	2	1	0
Olawaiye et al. 2009	10	10	10	3	3	3	1	0	1	1	0
Nishio et al. 2009	71	61	57	29	4	4	0	0	2	2	0
Cibula et al. 2009	24	20	17	9	6	6	1	0	2	3	0
Yao et al. 2010	10	10	10	NA	2	2	0	0	1	1	0
Li et al. 2011	64	62	59	10	2	2	0	0	1	0	1
Du et al. 2011	68	60	60	15	5	8	1[a]		3	2	2
Nick et al. 2012	25	24	21	NA	NA	3	1	1	0	1	0
Saso et al. 2012	30	30	NA	10	3	3	0	1	2	0	0
Muraji et al. 2012	23	21	20	NA	1	1	0	0	0	1	0
Wethington et al. 2012	101	81	70	38	28	31	3	6	16[b]		6
Karateke and Kabaca 2012	8	8	8	NA	3	3	0	1	1	1	0
Total	482	432	346	120	63	72	7	9	17	13	9

NA not available

[a]The timing of miscarriage was not described

[b]The timing of delivery was not described

specimen (Kyrgiou et al. 2006), which also holds true for post-radical trachelectomy pregnancies. As a shorter cervix can provide an easy route for ascending infections, which increase the risk of premature delivery, most clinicians aim to preserve at least 5 mm–1 cm of the endocervix during both procedures. There is no clear consensus regarding whether cervicoisthmic cerclage should be performed during radical trachelectomy or only after a patient has become pregnant.

Radical trachelectomy can also be performed via either a laparoscopic (Marchiole et al. 2007) or robotic approach (Persson et al. 2008). A previous retrospective study involving a relatively small number of patients suggested that these approaches are feasible, less invasive, and similarly effective, i.e., achieve comparable oncological outcomes, to conventional vaginal or abdominal approaches (Marchiole et al. 2007).

5 Surgical Complications

The intraoperative complications rate of VRT seems to be higher than that of ART (5.6 % vs. 0.7 %) (Pareja et al. 2013; Plante et al. 2011). The most common intraoperative complication of VRT is urinary tract damage. However, in comparisons of laparoscopic-assisted VRT versus laparoscopic-assisted vaginal radical hysterectomy (Marchiole et al. 2007) or ART versus ARH (Cao et al. 2013), all of the procedures exhibited similar perioperative complication rates, indicating that radical trachelectomy can be performed safely in carefully selected cases of early-stage cervical cancer.

The immediate postoperative complications associated with radical trachelectomy include bladder dysfunction, lymphedema, and lymphocele, which are comparable to the complications associated with RH (Pareja et al. 2013). In addition, the specific long-term postoperative complications associated with radical trachelectomy include cervical stenosis, dyspareunia, dysmenorrhea, prolonged amenorrhea, and chronic discharge. Similar rates of these complications are seen after VRT and ART (Beiner and Covens 2007; Cao et al. 2013; Pareja et al. 2013).

6 Adjuvant Treatments

The recommendations for post-trachelectomy adjuvant therapy are based on the presence/absence of pathological risk factors, such as nodal metastasis, parametrial involvement, LVSI, or DSI. Clinicians have to recognize that adjuvant radiotherapy affects patients' fertility (Beiner and Covens 2007; Hertel et al. 2006; Marchiole et al. 2007). Chemotherapy is an alternative adjuvant therapy. However, the clinical efficacy of adjuvant chemotherapy remains unclear.

7 Radical Trachelectomy for Tumors Larger Than 2 cm in Diameter

As the ART is more radical than VRT (Ungár et al. 2005; Wethington et al. 2012), it might have broader indications than other types of trachelectomy. However, in patients with larger tumors, radiotherapy is often indicated postoperatively because of the patient's pathological risk factors, which usually results in a loss of fertility.

Neoadjuvant chemotherapy (NACT) is the only way to reduce the size of cervical tumors, which might allow some patients with bulky tumors to undergo radical trachelectomy. Recent retrospective studies have suggested that NACT followed by radical trachelectomy is feasible and effective (Plante 2015). However, the oncological and reproductive issues have not been fully investigated. To draw a definitive conclusion regarding the benefits of NACT, further large-scale prospective studies are needed.

8 Hysterectomy in the Post-Childbearing Period

So far, there is no evidence that hysterectomy has beneficial effects in patients that do not want any more children.

9 Reproductive Issues

9.1 Fertility Issues

There is no clear consensus about the optimal interval between radical trachelectomy and attempts to get pregnant. However, as the tissue healing process can last at least 3 months, most authors suggest that patients should wait for 6–12 months before attempting to get pregnant.

Fertility might be impaired after radical trachelectomy because of anatomical and physiological changes, such as adhesion, cervical stenosis, and a loss of cervical function. In addition, the impact of pre-radical trachelectomy NACT on fertility remains unknown; however, a retrospective study found that 50 % of patients who received NACT followed by trachelectomy and retained their fertility subsequently became pregnant (Robova et al. 2014).

The pregnancy outcomes seen in previous studies are summarized in Tables 3 and 4. Among the women who attempted to get pregnant after VRT, 73.0 % (116 out of 159 women) were able to conceive, which is higher than the 45 % (54 out of 120 women) observed in the women who underwent ART. The reasons for the worse fertility outcomes of the ART group remain to be elucidated.

9.2 Obstetric Outcomes

Clinicians should inform patients who undergo radical trachelectomy that post-radical trachelectomy pregnancies are associated with an increased risk of obstetric complications.

As shown in Tables 3 and 4, the first-trimester miscarriage rate was 19.6 % (96 of 489 pregnancies) in the VRT group and 11.0 % (7 of 64 pregnancies) in the ART group, which are comparable to those of the general population. However, the second-trimester miscarriage rates of the patients in the VRT (8.4 %; 41 out of 489 pregnancies) and ART groups (14.1 %; 9 out of 64 pregnancies) were higher than that observed in the general population. Of the women who reached the third trimester, roughly two-thirds delivered their babies at term, and the remaining women (37.8 %) delivered prematurely (Tables 3 and 4). At present, there are no effective interventions for preventing preterm labor or preterm premature rupture of membranes.

9.3 Cesarean Section for Women Who Undergo Radical Trachelectomy

Cesarean section should be selected as the mode of delivery after radical trachelectomy. However, the optimal timing of cesarean section remains unclear. Moreover, it is disputed whether a low transverse incision or a low vertical incision should be performed in such cases.

10 Oocyte Cryopreservation for Women with Advanced Disease

Oocyte cryopreservation has been proposed to be an option for patients who are at risk of infertility due to RH or gonadotoxic adjuvant treatment. However, it is recommended that patients should be counseled about the current lack of data about the efficacy, risks, and costs of oocyte cryopreservation (Oocyte cryopreservation. Committee Opinion No. 584. American College of Obstetricians and Gynecologists).

11 Conclusion

Previous studies have shown that trachelectomy is a safe and feasible procedure and produces good oncological and reproductive outcomes in

patients with early-stage cervical cancer. To optimize the fertility and oncological outcomes of such patients, the strict indications for radical trachelectomy should be emphasized.

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Management of Cervical Dysplasia

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Abstract

Abnormal cervical screening tests are diagnosed in millions of women each year in the United States. In some, the abnormality is indicative of cervical dysplasia or even invasive cervical cancer. The work-up of an abnormal cervical screening test includes colposcopy and cervical biopsies. Based on those results, treatment for cervical dysplasia can consist of observation or intervention with an excisional biopsy. In deciding to intervene aggressively, one must consider special circumstances including patient age, desire for future fertility, and concurrent pregnancy. Understanding the role human papillomavirus (HPV) plays in cancer development has led to advancements in detection and treatment of cervical dysplasia. Both preventative and therapeutic vaccinations against HPV provide promise in decreasing the number of women affected by this disease. This chapter highlights key changes in the recent ASCCP guidelines including the importance of conservative management among younger women as well as recommendations on the proper utilization of HPV cotesting. The rationale for HPV vaccination is also discussed.

Keywords

Human papillomavirus • Cervical intraepithelial neoplasia • Adenocarcinoma in situ • Loop electrosurgical excision procedure • Cold-knife cone

1 Introduction

Since the 1940s, the Pap smear has provided practitioners an opportunity to diagnose cervical dysplasia and prevent cancer development. From 1973 to 2007, invasive cervical cancer incidence declined by 54 % in the United States (Adegoke et al. 2012). Furthermore, coordinated testing for human papillomavirus (HPV) has enabled healthcare providers the ability to appropriately triage patients based on risk. HPV infection is common and does not always cause cervical dysplasia; however, recognition and early intervention of high-risk HPV-related changes may prevent progression to cancer. In addition, early administration of vaccines against certain types of high-risk HPV could diminish the number of people diagnosed with cervical cancer precursors (Baldur-Felskov et al. 2014).

In the United States, there are an estimated two million abnormal cytology tests each year (Insinga et al. 2004). Among these women, 175,000 cervical intraepithelial neoplasia (CIN) 1 and 225,000 CIN 2/CIN 3 diagnoses are made. Progression from CIN to invasive cervical cancer is a slow process taking between 8.1 and 12.6 years for CIN 3 to progress to invasive cancer (ACOG Bulletin #140, December 2013). Despite advancements in the diagnosis and treatment of cervical dysplasia, cervical cancer continues to claim more than 4,000 lives each year in the United States http://seer.cancer.gov/statfacts/html/cervix.html. The body of knowledge on HPV, cervical dysplasia, and cervical cancer continues to grow bringing potential to decrease the number of deaths from cervical cancer each year.

The focus of this chapter is to provide readers with the most pertinent information on cervical dysplasia and, in turn, enable them to impart accurate and helpful information on their patients.

2 Cervical Cytology

Cervical cytology refers to cells that are obtained from the surface of the cervix and ideally include cells from the transformation zone of the cervix. Using a spatula and/or brush, cellular material from the cervix can be either spread and fixed directly onto a slide or transferred into a fixative liquid. In detecting precancerous lesions, the conventional Pap test using a slide- and liquid-based cytology proves to be equally sensitive and specific (Arbyn et al. 2008). Overall, sensitivity and specificity for cytologic testing for cervical dysplasia are about 60 % and 70 %, respectively (Nanda et al. 2000).

In an effort to standardize diagnosis and treatment, Bethesda 2001 developed terminology in the evaluation of cervical cytology. Management guidelines are based on these interpretations. The following information is adapted from the 2001 Bethesda system (Solomon et al. 2002). For any given cytologic sample, pathologists provide information on **specimen adequacy** and give an **interpretation/result**. Adequacy refers to whether the specimen is satisfactory for evaluation or unsatisfactory for evaluation. Interpretation can either reflect that the specimen is "negative for intraepithelial lesion or malignancy" or specify a type of epithelial cell abnormality. The most common cytologic abnormality is "atypical squamous cells" (ASC). Women with ASC have a 10–20 % risk of underlying CIN 2–3 and 1 in 1000 risk of invasive cancer. The category is further subdivided between "atypical squamous cells of undetermined significance" (ASC-US) and "cannot exclude HSIL" (ASC-H) (Solomon et al. 2002).

Squamous intraepithelial lesions are categorized in a two-tier system. Low-grade squamous intraepithelial lesions (LSIL) refer to mild dysplastic or HPV-related changes and frequently correspond to a histologic diagnosis of CIN 1. High-grade squamous intraepithelial lesions (HSIL) refer to moderate and severe dysplasia and typically correspond to a histologic diagnosis of CIN 2 or CIN 3. Squamous cell carcinoma can be detected by cytology; however, confirmation should be pursued with a biopsy for histologic diagnosis (Solomon et al. 2002).

Atypical glandular cells (AGC) refer to a glandular abnormality that could be arising from the cervix, endocervix, or endometrium. This diagnosis reflects a high-grade abnormality in 10–39 %

of cases. "Atypical glandular cells, favor neoplastic," endocervical adenocarcinoma in situ (ACIS), and adenocarcinoma are other examples of diagnoses included in this standard terminology (Solomon et al. 2002).

According to the American College of Obstetricians and Gynecologists (ACOG), cervical cancer screening with cervical cytology should being at age 21 regardless of age at coitarche. Between the ages of 21 and 29, cytology testing alone can be done every 3 years. After age 30, cytology alone every 3 years or combined cytology and HPV cotesting every 5 years can be recommended. In the absence of a history of abnormal cytology, screening can stop at age 65. If a patient undergoes hysterectomy for a benign gynecologic indication without history of cervical dysplasia, cervical cancer screening can be stopped after hysterectomy.

3 Human Papillomavirus

Papillomaviruses are a double-stranded, circular DNA genome virus with more than 100 different described subtypes. The viral DNA is divided into three regions: upstream regulatory region, early region, and late region. The early region of the genome includes six open reading frames, and, of these, E6 and E7 are required for the development of invasive cervical cancer. The E7 protein binds to the tumor suppressor retinoblastoma (Rb) gene blocking suppression and allowing cell proliferation. The E6 protein binds and degrades tumor suppressor P53 resulting in blockage of apoptosis and increased cell proliferation (Wright 2009). HPV types 16 and 18 are present in 70 % of diagnosed squamous cell carcinomas and over 80 % of adenocarcinomas (de Sanjose et al. 2010).

Persistent HPV is essential for the development of cervical cancer precursors and invasive cancer. When compared to cytology, high-risk HPV testing has proven to have higher sensitivity and reproducibility but less specificity (ACOG Bulletin #140, December 2013). At this time, HPV panels only detect a finite number of high-risk HPV types. Not all tests specify the exact HPV type that is positive in the panel, i.e., genotype. According to the College of American Pathologists, the most common indication for HPV testing remains reflex testing after ASC-US cytology; however, laboratories are reporting a general increase in the rate of cotesting (Zhao et al. 2015).

Transmission of HPV occurs via sexual exposure. Breaks in the skin and mucosal surfaces are susceptible to infection with the cervix being the most common site of transmission. Although condom use is still recommended for protection against HPV, external genitalia are susceptible to microtrauma and infection; thus, condom use is less protective than it is against other sexually transmitted infections. Vertical transmission from mother to infant is possible; however, the neonate can clear the vast majority of these infections within the first year of life (Erickson et al. 2013).

Overall prevalence of high-risk HPV is reported to be between 12 % and 15 % (Wright et al. 2012). The prevalence of HPV is highest in women 21–24 years old with a second spike occurring after menopause (Wright et al. 2012; Erickson et al. 2013). Most HPV infections will clear spontaneously; however, some infections will persist and cause cellular changes. Young women are more likely to clear HPV than older women. The clearance rate within 1 year of infection ranges from 40 % to 70 % and can reach a 2–5-year clearance rate of 100 % in young women (Erickson et al. 2013). Certain types of HPV are more virulent and are more likely to be persistent than other types. HPV 16 and HPV 18 are the most common HPV subtypes found in carcinoma of the cervix and found to be the most persistent (Wheeler 2013). HPV types considered to be oncogenic include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (Erickson et al. 2013).

3.1 Risk Factors

Risk factors for the development of dysplasia and invasive cervical cancer are interlinked with HPV infection and clinical conditions that make patients more susceptible to infection with HPV. Risk factors associated with HPV infection in

women include number of lifetime male sexual partners, early-onset sexual activity, coinfection with other sexually transmitted diseases, and current smoking (Erickson et al. 2013). Since HPV activity is dependent on the host immune system, immunosuppressed patients infected with HPV are at increased risk of developing cervical dysplasia and invasive cervical cancer. Immunosuppressed patients include patients with HIV, autoimmune disease, those who are status post organ transplant, and others who require chronic immunosuppressive therapies. These patients are recommended to have more frequent screening evaluation. Current recommendations are to screen these patients every 6 months for the first year after diagnosis of immunocompromised status followed by annual screening (Nguyen and Flowers 2013).

4 Management of Abnormal Screening Tests

The following management guidelines are based on the findings in the 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests and the ACOG Practice Bulletin on the management of abnormal cervical cancer screening test results and cervical cancer precursors (Wright 2007; ACOG Bulletin #140, December 2013; ASCCP guidelines). Most abnormal cytology results will require further evaluation of the cervix with **colposcopy**. The following are examples of abnormal results that do not require immediate colposcopy:

- For a woman older than 30 years of age with negative cervical cytology and her **first positive HPV** test, the ASCCP recommendation is to repeat cotesting in 1 year and proceed with colposcopy if cytology is abnormal or HPV remains positive at 1-year follow-up.
- For women with **ASC-US cytology and a negative HPV test**, ACOG recommends repeat cytology with HPV testing in 3 years.
- For women between the ages of **21 and 24 with ASC-US or LSIL**, HPV testing can be done. The patient should have repeat cytology 1 year after the test if positive and repeat cytology in 3 years if the test is negative.
- Unsatisfactory cytology with negative or unknown HPV results can be repeated in 2–4 months. Two consecutive unsatisfactory cytology results warrant evaluation with colposcopy.

Algorithms for the management of specific screening test results are available at the ASCCP website (http://www.asccp.org/Guidelines) and can also be downloaded as an application for mobile devices.

4.1 Colposcopy

Colposcopy is microscopic examination of the cervix under low power magnification after application of acetic acid. The goal of this procedure is to visually detect any cervical changes suspicious for precancerous transformation. The procedure consists of a speculum exam during which gauze is soaked with 3–5 % acetic acid and placed directly on the cervix for approximately 30 s to 1 min. After exposure to acetic acid, a reversible reaction occurs causing the abnormal cells to swell and turn white due to hyperchromatin within the nucleus of the dysplastic cells.

Identification of acetowhite epithelium (AWE) allows for directed biopsies of suspicious lesions. The transformation zone is identified, and a small cotton-tipped swab can be used to manipulate the cervical canal and identify whether the AWE extends into the canal. An endocervical speculum can be used for this part of the procedure. Other abnormal features to note include punctation, mosaic patterns that suggest underlying high-grade dysplasia, and abnormal neovascularization that could be an indication of possible invasive cancer.

In addition to the cervix, the upper vagina should be examined. Directed biopsies are performed with a sharp cervical biopsy device. A sharper device will lead to less manipulation and stretch of the cervical fibers and diminish pain. Bleeding is a risk of this procedure. Silver

nitrate and Monsel solution can be used to hamper bleeding; however, spotting and brown discharge are common after biopsies. Excellent photographs and additional descriptions of colposcopic findings can be found in text by Baggish (2003).

Even if colposcopic examination is negative for any abnormal findings, a single random biopsy can increase detection of high-grade disease in high-risk HPV-positive patients (Huh et al. 2014). It remains unclear why some lesions are not visible colposcopically and whether this reflects a difference in the biological or clinical nature of non-visible lesions as compared with visible lesions. Ultimately, studies show that colposcopy has similar sensitivity and specificity when compared to cervical cytology in detecting high-grade lesions. Women with limited access to screening cytology in under-resourced countries that cannot afford to implement routine HPV testing may benefit from immediate colposcopic examination. The limitation of "see-and-treat" methodology remains the possibility of overtreating (Nooh et al. 2015).

5 Types of Cervical Dysplasia

5.1 Cervical Intraepithelial Neoplasia

Cervical intraepithelial neoplasia (CIN) is a term used to describe a continuum of dysplastic changes in cervical intraepithelial tissue. These changes are precursors to cervical cancer development. The continuum consists of mild, moderate, and severe cellular changes referred to as CIN 1, 2, and 3, respectively. A histopathologic diagnosis of CIN depends on the level of nuclear abnormality, mitotic activity, and level of differentiation (Robboy et al. 2002).

In **CIN 1**, extensive differentiation can be seen in the upper two-thirds of the cervical epithelium. There is minimal amount of nuclear atypia and few, if any, mitotic figures that are located in the **basal third** of the epithelium (Robboy et al. 2002). CIN 1 has a high rate of regression and can be managed conservatively with repeat cytology and HPV testing 12 months after initial diagnosis. Patients should be counseled that this lesion usually represents a transient HPV infection and has very low premalignant potential. Over a period of 2 years, the risk of progression of CIN 1 to CIN 2 was 13 %, and the risk of progression of CIN 1 to CIN 3 was 8.9 % (ALTS 2003). If a patient has persistent CIN 1 for over 2 years, observation or excision is acceptable. Excision is recommended if the transformation zone cannot adequately be evaluated on colposcopy. In addition, if CIN 1 was found on endocervical curettage (ECC) at the time of colposcopy, ECC should be performed with the subsequent cytologic sampling (ACOG Bulletin #140, December 2013).

In **CIN 2**, mitotic figures are located in the **basal two-thirds** of the epithelium, differentiation can be seen in the upper half of the epithelium, and the nuclei are more atypical and larger than in CIN 1 (Robboy et al. 2002). Although CIN 2 can regress, patients should be counseled that 35 % persist and 22 % progress to CIN 3 (ACOG Bulletin #140, December 2013). Except in special populations, patients with CIN 2 are offered excision in an effort to prevent progression to CIN 3 and, ultimately, invasive cancer. In young age women, either close observation or ablation of the lesion can be considered.

In **CIN 3**, nuclear abnormalities and mitotic figures populate the **entire thickness** of the epithelium. The nuclei can occupy almost the entire cell and are bizarre in shape. Data on the natural history of CIN 3 revealed that 56 % persist and 14 % progress to invasive cancer (ACOG Bulletin #140, December 2013). The term carcinoma in situ (CIS) was included in prior terminology; however, this diagnosis is no longer used. Rather, that which was labeled as CIS is now considered CIN 3. Excisional biopsy is the preferred management for CIN 3.

5.2 Adenocarcinoma In Situ

Adenocarcinoma in situ (ACIS) describes a precursor lesion to invasive adenocarcinoma of the cervix. Pathologists describe ACIS as replacement of endocervical glandular cells with tall columnar cells with nuclear atypia and elevated

Table 1 Recommendations for follow-up after cone biopsy for cervical dysplasia

Cone (LEEP or CKC)	Internal margin	ECC	Desiring future fertility	Risk of residual dysplasia	Risk of microinvasion	Risk of frank invasion	Follow-Up
CIN 3	neg	neg	n/a	18 %	0 %	0 %	Cotesting in 1 year
CIN 3	neg	CIN 3	Yes	40 %	0 %	0 %	4–6-month cotesting with ECC
CIN 3	neg	CIN 3	No	40 %	0 %	0 %	4–6-month cotesting with ECC
CIN 3	CIN 3	neg	Yes	30 %	0 %	0 %	4–6-month cotesting with ECC
CIN 3	CIN 3	neg	No	30 %	0 %	0 %	4–6-month cotesting with ECC
CIN 3	CIN 3	CIN 3	Yes	44 %	19 %	11 %	4–6-month cotesting with ECC preferred; repeat CKC acceptable
CIN 3	CIN 3	CIN 3	<50, neg FF	22–44 %	Up to 17 %	0 %	4–6-month cotesting with ECC preferred; repeat CKC acceptable
CIN 3	CIN 3	CIN 3	>50/ postmenopausal	46 %	9 %	18 %	CKC - > clear margins = follow as above; CKC - > positive margins/ ECC - > hyst v. MRH
ACIS	neg	neg	Yes	14 %	0 %	0 %	6-month cotesting; recommend completion hyst after childbearing
ACIS	neg	neg	No	14 %	0 %	0 %	Hyst
ACIS	+	neg	No	40 %	7 %	0 %	CKC – > Hyst
ACIS	neg	+	No	80 %	20 %	0 %	CKC – > Hyst
ACIS	+	+	No	77 %	15 %	0 %	CKC – > Hyst
ACIS	Either +/–	Either +/–	Yes	59 %	13 %	0 %	CKC until margins negative; recommend completion hyst after childbearing

mitotic activity. Less prevalent than CIN, the management of ACIS has proven to be a challenge. Estimates for the risk of underlying malignancy can be up to 17 %. After biopsy diagnosis, all patients should have a cone biopsy to exclude the diagnosis of underlying cancer. Standard treatment for ACIS is hysterectomy; however, fertility-sparing measures can be taken in special circumstances (Tierney et al. 2014). See *Special Considerations* for information of fertility preservation.

5.3 Management of Dysplasia

In managing a diagnosis of cervical dysplasia, the simple objectives are to prevent progression to invasive cervical cancer and to exclude the presence of concurrent carcinoma. Management decisions can only be made after thorough review of cytologic and colposcopic findings.

5.3.1 Observation

As previously mentioned, CIN 1 can safely be monitored without excision. Given the high

likelihood of regression, ACOG recommends repeat cotesting 1 year from the diagnosis. For CIN 2, the risk of progression must be weighed against the risk to future pregnancies. Observation is preferred in women ages 21–24 and "young women." A "young woman" is considered someone in whom the risks to future pregnancies outweigh the risk of disease progression. Conservative management using serial cytologic sampling, HPV testing, and colposcopy at regular intervals appears to be appropriate in this population. Recommendations are for repeat exams every 6 months for at least the first year (ACOG Bulletin #140, December 2013).

5.3.2 Ablation

Ablative procedures for the treatment of cervical dysplasia include cryosurgery, CO_2 laser vaporization, and electrocoagulation. The primary benefits of these procedures are that they are cost-effective and simple. These methods are not commonly utilized secondary to their obvious disadvantages. Ablative procedures do not predictably destroy tissue and they do not provide a specimen. Therefore, diagnosis of an underlying cancer could be inadvertently overlooked (Morrow and Sideri 2013; Baggish 2003).

5.3.3 Excision

The objective of an excisional procedure is to treat the existing precancerous lesion and, if present, diagnose any underlying microinvasive disease. If a cone is not feasible secondary to distorted anatomy, one may proceed with a hysterectomy. The patient must be informed of the risk of invasive cancer that may result in postoperative adjuvant therapy or additional surgery.

The specimen should be evaluable for the presence or absence of dysplasia at the margins (endocervical and ectocervical). Post-excisional endocervical curettage (ECC) should be performed routinely. Information on the margin status and ECC has been shown to predict the presence of residual disease for both squamous and glandular lesions (Kobak et al. 1996; Tierney et al. 2014). Positive endocervical margins and positive ECC are more concerning than a positive ectocervical margin. Ectocervical lesions are more easily detected on Pap smear and colposcopy.

Follow-up recommendations are summarized in Table 1 (ACOG Bulletin #140, December 2013; Kobak et al. 1996; Tierney et al. 2014).

Following cone biopsy for CIN 3, ACOG recommends repeat cotesting in 1 year for those with negative margins and ECC. For those with positive margins and/or ECC, ACOG recommends closer follow-up with repeat cotesting in 4–6 months and repeat ECC at the time of cotesting. Providers and patients must understand that, although most who have positive margins and/or ECC will not have recurrent or persist cervical dysplasia, those with both positive margins and positive ECC are at the highest risk of recurrence/persistence. Some patients will find that the risk is unacceptable and will be more comfortable with a follow-up procedure such as a repeat cone.

Age should be considered when counseling patients on risk of persistent cervical dysplasia and invasive cervical cancer. Data suggests that women over 50 years of age (or postmenopausal women) who have a positive endocervical cone margin and a positive ECC have a 9–18 % risk of having invasive cervical cancer. These women should have a repeat excisional procedure. If the margins and ECC are negative on the second conization, follow-up with cotesting and an ECC in 4–6 months is reasonable. If margins and/or ECC are positive on the second conization, recommendations are for repeat conization. If repeat conization is not feasible secondary to anatomy, the patient must be counseled on risk of concurrent cancer and consider a modified radical hysterectomy versus a simple hysterectomy (Kobak et al. 1996).

The following text will describe both cold-knife cone (CKC) and loop electrosurgical excision procedure (LEEP) as methods of excision. These methods have been found to be equivalent in treating dysplasia (Huang and Hwang 1999). An important risk of excisional procedures is the risk to future pregnancies. Women who undergo these procedures are at an increased risk of having cervical stenosis, cervical shortening, and preterm birth. Studies show about a 30 % increased incidence of preterm birth in patients who have

undergone an excisional procedure (Frey and Conner 2015).

Cold-knife cone (**CKC**), otherwise known as scalpel cone or sharp conization, is removal of a cone-shaped piece of tissue from the cervix. The specimen includes the transformation zone and a segment of the endocervical canal. The cone is typically 1.5–2.5 cm in height. The procedure is performed under anesthesia in the operating room. After colposcopy and/or Lugol application, the surgeon can determine the size and shape of the cone based on the extent of dysplasia. A sound should be used to determine the cervical length and direction of the canal. After traction sutures are placed and vasopressin is injected intracervically in select cases, a #15 or #11 blade is pushed into the cervical stroma at an angle that points toward the cervical canal. A single-tooth tenaculum can be applied to 12 and 6 o'clock to stabilize the cervix. An Allis clamp can be used to gently manipulate the specimen without losing orientation. After removal of the specimen from the cervix, suture is used to mark the 12 o'clock location to orient the specimen. An endocervical curettage follows the removal of the cone biopsy using a Kevorkian curette and endocervical cytobrush. Bleeding from the cone bed can usually be controlled with cautery. Monsel solution, Surgicel packing, and various suturing techniques can also be utilized (Morrow and Sideri 2013). The advantage of CKC is lack of thermal artifact allowing the pathologist to confidently comment on margin status. The disadvantage is that it requires anesthesia and an operating room to complete with possible increased risk of bleeding.

When compared with CKC, the **LEEP** procedure also provides a specimen for pathologic examination; however, it is an in-office procedure that is simple and inexpensive. In the office, the procedure is performed using local anesthetic with 1–2 % lidocaine injected directly into the cervical stroma. Colposcopy with acetic acid application is performed followed by Lugol application if indicated. The appropriate loop electrode is selected based on the size of the lesion. Power is set at between 40 and 50 W using a blend of cutting and coagulation current. The loop is passed through the cervical stroma at a steady rate, careful to avoid both bleeding and thermal effect to the specimen. Endocervical curettage is performed after the specimen is obtained. Hemostasis can be achieved with the rollerball and Monsel solution (Morrow and Sideri 2013).

5.3.4 Pharmacological Agents

The utility of topical agents in the treatment of cervical dysplasia is under investigation. Both 5-flourouracil (5-FU) and imiquimod have been used as agents to treat vulvar dysplasia and are being considered in the treatment of cervical precancerous lesions. 5-FU is an antimetabolite that inhibits thymidylate synthase causing cell death. In young women, 5-FU used to treat CIN 2 was shown to cause regression in 93 % of patients as compared to 56 % regression among those who were observed. This data came from a randomized controlled trial of two groups (treatment with 5-FU versus observation) over a 6-month treatment period during which there were no reported moderate to severe side effects (Rahangdale et al. 2014). More common side effects include pain, burning, and dermatitis. Suggested treatment dosing is 2 g via transvaginal applicator every 2 weeks for a total of 8 doses. The use of 5-FU in this setting is considered off-label and should only be considered in young patients attempting to conserve fertility with informed consent.

The topical immune-response modulator imiquimod is another agent that could to be efficacious in treating cervical dysplasia. Imiquimod activates the innate immune system via a toll-like receptor (TLR-7) and recruits macrophages, natural killer cells, and B-lymphocytes to the treated site. In the treatment of CIN 2–3, remission rates in patients treated with imiquimod were higher when compared with those observed over time; 73 % of those treated with imiquimod regressed while only 39 % of those treated with placebo regressed (Grimm et al. 2012). Common side effects of imiquimod include mild pruritus, pain, and a systemic "flu-like" reaction. Long-term and larger studies are needed to determine the ideal therapeutic application of these agents. With more investigation, topical agents could prove to be a reasonable alternative to excisional biopsy in

those who plan to reduce risk of preterm birth in future pregnancies.

5.3.5 Hysterectomy

Hysterectomy is not a standard treatment as primary therapy for CIN 2 or CIN 3 (ACOG Bulletin #140, December 2013). After diagnosis of recurrent disease, repeat excisional biopsy is preferred to exclude the presence of invasive cancer. Indications for hysterectomy include:

- Recurrent disease after evaluation with repeat excisional procedure
- Situations in which a repeat excisional procedure is not feasible due to distorted anatomy, i.e., minimal residual cervix or a flush cervix

For a diagnosis of ACIS, hysterectomy is standard of care in women who have completed childbearing. However, excisional biopsy needs to be preformed prior to hysterectomy to rule out concurrent invasive cancer.

5.4 Special Considerations

5.4.1 Dysplasia in Pregnancy

For women with dysplasia diagnosed during pregnancy, most dysplasia will regress, and evolution to cancer is extremely rare (Fader et al. 2010). Evidence-based guidelines for management of cervical dysplasia in pregnancy suggest cervical biopsies should only be performed if frank cancer is suspected on colposcopy. Repeat colposcopy at 6 weeks postpartum is recommended. If a biopsy is performed with a result of CIN 2 or CIN 3, colposcopy no sooner than every 12 weeks can be performed. A biopsy should only be done if the lesion appears to worsen (ACOG Bulletin #140, December 2013).

5.4.2 Fertility-Sparing and ACIS

For those who desire to maintain future fertility, patients with a diagnosis of ACIS should have a cone biopsy to exclude the diagnosis of underlying cancer. If cone margins or ECC is positive for ACIS, repeat cone can be performed in these patients. If both margins and ECC are negative, data show that no patients had underlying cancer and about 14 % had residual ACIS. Patients should be closely monitored with cotesting every 6 months (Tierney et al. 2014).

5.5 Human Papillomavirus Prevention

Vaccination against HPV has demonstrated efficacy in preventing development of cervical dysplasia. Additionally, therapeutic vaccines have emerged and may change the future treatment landscape for cervical dysplasia. HPV has two capsid proteins (L1 and L2), and the HPV vaccine is made with recombinant L1 protein (a virus-like particle) to target the L1 capsid protein (Erickson et al. 2013). Currently, there are three FDA-approved HPV vaccines available in the United States. Available vaccines include a bivalent vaccine targeting HPV 16 and HPV 18 (Cervarix by GlaxoSmithKline, Brentford, United Kingdom), quadrivalent (Gardasil by Merck & Co Inc., Kenilworth, NJ, USA), and 9-valent (9vHPV by Merck & Co Inc., Kenilworth, NI, USA) types.

The quadrivalent vaccine Gardasil protects against two high-risk types of HPV (16 and 18) and two low-risk types of HPV commonly seen in patients with genital warts (6 and 11). Administration is indicated to prevent HPV-related genital warts and precancerous and cancerous lesions in women and men for ages 9 through 26 years www.merckvaccines.com/products/gardisil. HPV vaccines have the secondary benefit of protection against all HPV-related cancers including some head and neck cancers and anal and penile cancer. In those who have been vaccinated, there is a 60 % risk reduction for atypia, and the risk of CIN 2/CIN3 and CIN 3 is reduced up to 80 % (Baldur-Felskov et al. 2014). Women vaccinated at an older age have been shown to have less of a risk reduction presumably because they have previously been exposed to HPV 16/HPV 18. Recommendations are to advocate for vaccination before sexual activity (Baldur-Felskov et al. 2014; Mahmud et al. 2014). However, current

recommendations are to vaccinate all people between the ages of 9 and 26 regardless of sexual history or history of diagnosed cervical dysplasia. Indications for HPV vaccination in women older than 26 need to be developed in the future.

The 9-valent HPV (9vHPV) vaccine builds immunity against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The efficacy against types 6, 11, 16, and 18 has been shown to be equivalent to the quadrivalent vaccine. 9vHPV has been shown to prevent disease associated with the HPV types covered by the vaccine (Joura et al. 2015).

For those who have been vaccinated, screening recommendations do not change (ACOG Bulletin #140, December 2013). Long-term follow-up is needed to see the effect these vaccines have on cervical and vulvar cancer prevalence as well as other HPV-related cancers such as head and neck and anal and penile cancer prevalence.

The use of therapeutic vaccinations in the treatment of infection-mediated precancerous and cancerous lesions is under investigation. For those patients with high-grade dysplasia, the efficacy of the available vaccines proves to be low (Mahmud et al. 2014). A therapeutic vaccine elicits an adaptive immune response against the lesion. A recent phase 2 trial shows promising results for a therapeutic vaccine, VGX-3100 (Inovio Pharmaceuticals, Inc, Plymouth Meeting, PA, USA), against cervical dysplasia (CIN 2/3). These findings lend hope for a nonsurgical treatment of cervical dysplasia (Trimble et al. 2015).

6 Conclusion

In conclusion, cervical cancer screening with cytology and HPV testing has decreased the overall incidence of cervical cancer over the last century. The standardization of dysplasia management has been facilitated by easily accessible ASCCP guidelines. Treatment of cervical dysplasia has remained relatively consistent; however, given the high rate of regression in certain populations, more conservative management has been recommended in younger patients and pregnant patients. Ultimately, ACOG and ASCCP give guidelines for the management of dysplasia; however, care should still be individualized. Recommendations are based on "acceptable risk" meaning that negative screening does not guarantee the absence of an abnormality. Worrisome findings may warrant close follow-up and more frequent exams. Informed consent is key. Patients need to know the pathophysiology of HPV-related disease, risk of disease progression, and risks of invasive intervention. There are few preventative interventions for patients once they are diagnosed with HPV. Gynecologic and pediatric care providers should take every opportunity to discuss risk reduction and the benefits of HPV vaccination.

7 Cross-References

▶ Pathology

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Diagnosis and Management of Vaginal Cancer

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Contents

Abstract

Primary malignancies of the vagina are rare, comprising only about 1–4 % of all gynecologic malignancies. The majority of vaginal cancers are metastases from other sites. Among primary vaginal tumors, squamous cell carcinoma (SCC) is the most common, followed by adenocarcinoma, melanoma, and other rare histologies. Squamous cell carcinomas are frequently associated with chronic human papillomavirus (HPV) infection, whereas adenocarcinomas are associated with in utero diethylstilbestrol (DES) exposure. Vaginal intraepithelial neoplasia (VAIN) is a premalignant condition thought to progress to invasive squamous cell carcinoma if untreated. Vaginal intraepithelial neoplasia is generally asymptomatic and diagnosed by abnormal vaginal cytology followed by vaginal colposcopy and biopsies. Most vaginal cancers present with abnormal vaginal bleeding or a vaginal mass. Diagnosis is made by physical exam and confirmatory biopsy. Treatment of vaginal cancer depends on the primary histology, stage at diagnosis, and patient characteristics. Treatment options include surgical excision, radiation therapy, and chemotherapy. The majority of vaginal cancers are treated with radiation, frequently in combination with chemotherapy. Prognosis varies depending on underlying histology and stage at presentation; however, with advances in radiation

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techniques, survival rates are similar to those seen in cervical cancer.

Keywords
Vaginal intraepithelial neoplasia (VAIN) • Vaginal squamous cell carcinoma • Vaginal adenocarcinoma • Vaginal melanoma • Vaginal rhabdomyosarcoma

1 Introduction

Primary malignancies of the vagina are quite rare, comprising only about 1–4 % of all gynecologic malignancies (Siegel et al. 2015). In the USA, approximately 4000 women are diagnosed with vaginal cancer each year, and approximately 900 women die of the disease (Siegel et al. 2015). The majority of cancers involving the vagina are actually secondary metastases or direct extensions from other primary sites. In a series of 355 invasive carcinomas involving the vagina, only 58 (16 %) represented primary vaginal lesions. Among secondary sites metastatic to the vagina, the cervix was most common (32 %), followed by the endometrium (18 %), colon and rectum (9 %), ovary (6 %), vulva (6 %), bladder and urethra (4 %) (Fu and Reagan 1989).

In this chapter, we will focus on the diagnosis and management of primary vaginal malignant neoplasms and premalignant conditions. Due to the rarity of the disease, most treatment strategies are derived from small retrospective case series and extrapolated from prospective studies for the treatment of cervical and anal cancers. Squamous cell carcinoma is the most common and well-studied histology, representing 65–79 % of vaginal cancers in two large cancer registry studies (Creasman et al. 1998; Shah et al. 2009). Adenocarcinoma is the second most common histology representing 9–14 % of tumors, followed by melanoma (3–6 %) and other rare histologies including mesenchymal, germ cell, neuroendocrine, and hematologic cell types collectively accounting for the remaining 4–15 % (Creasman et al. 1998; Shah et al. 2009). The majority of vaginal cancers are treated with radiation, frequently in combination with chemotherapy. Prognosis varies depending on underlying histology and stage at presentation; however, with advances in radiation techniques, survival rates are similar to those seen in cervical cancer.

2 Vaginal Anatomy

The vagina is a fibro-muscular, distensible tube extending from the uterine cervix superiorly to the vestibule of the vagina, vulva, and perineum inferiorly. Embryologically, the vagina is formed by fusion of the urogenital sinus epithelium inferiorly with the mullerian ducts superiorly. Structural support for the vagina includes the cardinal and uterosacral ligaments superiorly and the muscular supports of the pelvic floor including the levator ani, the bulbospongiosus muscle, and urogenital diaphragm. The vagina shares fascial support anteriorly with the bladder and posteriorly with the rectum. Between these attachments, the lateral vaginal wall opens into the paravaginal space. The vaginal fornix describes the recesses around the uterine cervix and can be divided into anterior, posterior, and lateral regions. The posterior fornix is the largest and is separated from the rectum by a fold of peritoneum, forming the pouch of Douglas.

The vaginal wall consists of three layers: the mucosa, the muscularis, and the adventitia. The mucosa is lined by the nonkeratinized stratified squamous epithelium, rich in glycogen and estrogen. There are no glands or crypts in the vagina, and the mucosa is primarily lubricated by cervical glands. Vaginal atrophy, characterized by mucosal thinning and blunting of the vaginal rugae, is common in low estrogen states such as prior to onset of puberty and after menopause. Underlying the epithelial basement membrane is the submucosal layer, highly vascular and rich in lymphatics. The muscularis layer consists of smooth muscle fibers, and adventitia is a thin layer of connective tissue continuous with the adventitia layer of other surrounding organs.

The arterial supply of the upper vagina comes from the internal iliac artery frequently off a trunk shared with the uterine artery, called vaginal

artery, while the middle and lower portions of the vagina are supplied by branches of the middle rectal and internal pudendal arteries. Venous drainage is facilitated by vaginal venous plexuses in the lateral vagina which drain into the internal iliac vein. The vagina is innervated by nerves derived from the inferior hypogastric plexus.

Classically, lymphatic vessels from the upper 2/3 of the vagina drain into the internal iliac and external iliac lymph nodes, while vessels from the lower 1/3 drain into the superficial inguinal lymph nodes via lymphatic channels in the lateral vagina (Plentl and Friedman 1971). Posterior vaginal lesions may also drain into para-rectal nodes (Plentl and Friedman 1971).

3 Natural History

Most data about the natural history of vaginal carcinoma emanates from early case reports where few treatment modalities were available, and many patients presented with advanced disease. In a compilation of early case series, Plentl and Friedman report that of 1204 vaginal cancer cases, 57.2 % were located on the posterior wall, 26.9 % on the anterior wall, and 15.9 % on the lateral wall (Plentl and Friedman 1971). Among 743 cases with data available, 50.7 % of tumors were located in the upper 1/3 of the vagina, 18.8 % in the middle 1/3, and 30.4 % in the lower 1/3. VAIN also has a predilection for the upper vagina, which is thought to be due to an HPV-related field effect in patients with cervical HPV infections.

Vaginal cancers may spread by contiguous growth and local invasion, lymphatic drainage, and hematogenously. Because of closely approximated structures including the urethra, bladder, rectum, and pelvic bones, locally advanced disease is generally symptomatic and carries a high rate of morbidity. Due to the rich lymphatic drainage of the vagina, lymph node metastases occur relatively early in the disease. By contrast, hematogenous dissemination to distant sites, such as the liver, lung, or bone, occurs late in the disease process.

4 Epidemiology

Vaginal squamous cell carcinoma is primarily a disease of older women, with peak incidence between ages 60 and 80 (Creasman et al. 1998; Shah et al. 2009). Vaginal squamous cell carcinoma is considered to be an HPV-related disease and shares many risk factors with other HPV-related squamous cell carcinomas, including prior documented HPV infection (particularly HPV 16), history of cervical or vulvar dysplasia (CIN or VIN), immunosuppression, five or more sexual partners or sexual debut prior to age 17, smoking, and low socioeconomic status (Daling et al. 2002). VAIN and squamous cell carcinomas are strongly associated with a prior history of cervical cancer. Prior radiation therapy (Hellman et al. 2004) and chronic vaginal irritation related to pelvic organ prolapse and pessary use have also been proposed as possible risk factors (Wang et al. 2014).

Vaginal adenocarcinoma is associated with precursor lesions including vaginal adenosis, endometriosis, and mesonephric rests. Vaginal clear cell carcinoma, associated with in utero diethylstilbestrol (DES) exposure is the most commonly described form in the literature. DES is a nonsteroidal estrogen that has been implicated in congenital reproductive tract abnormalities including persistence of vaginal glandular tissue in a condition called vaginal adenosis. In review of registry cases, Herbst reported that among women exposed to DES in utero, the risk of clear cell carcinoma of the vagina or cervix was approximately 1/1000, with age at diagnosis ranged from 7 to 34 years, with peak incidence at age 14–22 (Herbst and Andersond 1990). Vaginal adenosis occurred in 45 %, and structural genital tract anomalies in 25 %. The incidence of vaginal clear cell carcinoma has declined significantly since the 1990s. Non-DES-related vaginal adenocarcinomas occur in older women, with a median age at diagnosis of 54 (Frank et al. 2007).

A small subset of vaginal cancer has a predilection for the pediatric population. Vaginal rhabdomyosarcoma, also known as sarcoma botryoides, accounts for approximately 4 % of

rhabdomyosarcomas, which are the most common tumors in childhood. The median age at presentation is 16.3 months (Magné et al. 2008). Vaginal and cervical yolk sac tumors, also known as endodermal sinus tumors, are another rare vaginal tumor of childhood. Only about 100 cases have been reported in the literature, all diagnosed prior to age 3.

5 Signs and Symptoms

Approximately 15–17 % of vaginal cancers are asymptomatic and identified by abnormal cytology or incidental mass on routine pelvic examination (Eddy et al. 1991; Hellman et al. 2004). Abnormal vaginal bleeding is the most commonly reported symptom of invasive carcinoma; however, abnormal vaginal discharge and dysuria are also frequently reported. In the case of more advanced disease, patients may present with pain, the sensation of a mass, or symptoms related to the involvement of adjacent pelvic organs. Tumors involving the bladder may present with urinary incontinence or retention, hematuria, urgency, or frequency. Tumors involving the rectum may present with constipation, tenesmus, or rectal bleeding. Sarcoma botryoides presents with a characteristic edematous, grape-like mass protruding from the vagina.

Vaginal intraepithelial neoplasia (VAIN) is generally asymptomatic, but may present with abnormal vaginal discharge which is often the result of a coincidental vaginitis. Most cases of VAIN are diagnosed after abnormal vaginal cytology in women who have a history of cervical dysplasia

6 Diagnosis

Vaginal cancer should be diagnosed after a thorough focused history and physical exam, careful inspection of the vagina, confirmatory biopsies, and exclusion of more common gynecologic malignancies which may have metastasized to the vaginal mucosa. According to the International Federation of Gynecology and Obstetrics (FIGO) definitions, any vaginal lesion also involving the cervix or the vulva should be classified as a cervical or vulvar primary cancer, respectively (Hacker et al. 2015). Similarly, in women with a prior history of cervical carcinoma, a vaginal carcinoma lesion should not be considered a second primary unless the patient has been without evidence of disease for at least 5 years (Hacker et al. 2015).

Inquiry of clinical history should include symptoms and risk factors associated with vaginal carcinoma and a complete past medical and gynecological history. Physical examination should focus on evaluation of potential metastatic sites, with particular care to palpate the inguinal and supraclavicular lymph nodes, which may be enlarged in advanced disease.

During pelvic examination, the vulva and anus should be carefully inspected for HPV-related lesions, with care to visualize folds of the labia and the vaginal vestibule prior to speculum insertion. The entire vaginal surface should be visualized, which may require an exam under anesthesia in women with locally advanced disease or vaginal stenosis secondary to severe vaginal atrophy or prior radiation. Most vaginal cancers are located in the upper vagina, frequently on the posterior wall. A speculum examination should be performed with care to inspect the anterior and posterior fornix as well as the distal vagina. Lesions in the distal anterior and posterior vagina may be obscured by the blades of the speculum unless the speculum is gently rotated to expose the circumferential surface of the vagina. Small lesions may be difficult to identify in parous or obese women with redundant vaginal folds. In women who have had a prior hysterectomy, lesions also may be concealed by folds of mucosa buried within the vaginal cuff closure. Partial upper vaginectomy may be required to adequately evaluate these patients.

Vaginal cancers are frequently exophytic, papillary appearing tumors, but infiltrating, ulcerative and flat spreading forms are also seen (Morrow and Curtin 1998). Carcinomas arising in the setting of extensive VAIN may be multifocal. Any visible lesions should be evaluated with full-thickness mucosal biopsies. Vaginal cytology

may also be useful to identify cellular atypia, but should not be used alone to evaluate for VAIN or vaginal malignancies. Any woman with a suspicious vaginal lesion who has not had a total hysterectomy should also have consideration of cervical biopsies and endocervical sampling to evaluate for an occult cervical malignancy. Similarly, women with abnormal bleeding and an intact uterus should have an endometrial biopsy or dilation and curettage to evaluate for endometrial cancer. A bimanual exam should be performed to palpate the size and extent of an intravaginal mass and assess for any pelvic masses. This exam should be followed by a rectovaginal exam to identify gross invasion through the rectal mucosa, tumor infiltration of the rectovaginal septum, and parametrial or pelvic sidewall involvement. When locally advanced disease is suspected based on the size and location of the primary tumor, cystourethroscopy and/or proctoscopy are indicated. Biopsies should be obtained if there is any question of mucosal bowel or bladder involvement. Sigmoidoscopy may also be considered for women with large tumors in the posterior vaginal fornix that are suspected to extend into the pelvis.

All patients with abnormal cytology but no grossly visible lesion should be further evaluated with vaginal colposcopy. Some providers advocate colposcopy for all cases of vaginal carcinoma in order to visualize any areas of occult mucosal involvement or associated dysplasia. Colposcopy can be performed in the office during initial examination and may be repeated in the operating room as needed to guide biopsies or excision of lesions identified. Acetic acid solution should be liberally applied to the vagina, and the mucosa should be inspected under magnification using a colposcope. Lugol's iodine solution may be a useful adjunct to identify nonstaining mucosa. Colposcopically abnormal mucosa should be biopsied for diagnosis. When there is a question of high-grade dysplasia versus invasive carcinoma, lesions should be excised, as a large superficial lesion may contain a small focus of deeper invasion that could be missed on biopsy alone. A complete upper vaginectomy may be necessary in order to adequately rule out invasive carcinoma in the setting of multifocal or extensive high-grade VAIN. In a series of sequential upper vaginectomies for VAIN2 or VAIN3 from 1985 to 2004, Indermaur et al. reported that 12/105 (12 %) had a previously unsuspected invasive carcinoma (Indermaur et al. 2005).

Table 1 FIGO stage and 5-year overall survival rates for vaginal cancer

FIGO stage[a]	Definition	Creasman et al. 1998[b] (NCDB data, $n = 4885$)	Shah et al. 2009[c] (SEER data, $n = 2149$)
I	Limited to the vaginal wall	73 %	84 %
II	Involving subvaginal tissue	58 %	75 %
III	Pelvic sidewall involvement	36 % (stages III and IV)	57 % (stages III and IV)
IVA	Bladder or rectum invasion or extension beyond the pelvis		
IVB	Distant metastases		

Compiled from:
[a]Hacker et al. (2015)
[b]Creasman et al. (1998)
[c]Shah et al. (2009)

7 Evaluation and Staging

Similar to cervical cancer, vaginal cancer staging is clinical. Two commonly used staging systems are defined by the International Federation of Gynecology and Obstetrics (FIGO) and American Joint Committee on Cancer (AJCC) TNM staging system (Edge et al. 2010; Hacker et al. 2015). In both systems stage I/T1 describes tumors confined to the vaginal wall; stage II/T2 tumors invade the paravaginal tissues; stage III/T3 involves the pelvic sidewall; stage IV/T4 invades the bladder or rectal mucosa; and distant metastases (M) are labeled stage IVB (Table 1).

Lymph node involvement is not directly addressed in the FIGO system, whereas in the AJCC system it is designated by N, and all patients with positive pelvic or inguinal lymph nodes are assigned to N1 (clinical stage III). Metastatic sites (AJCC designation M1) include, but are not limited to, aortic lymph nodes, lungs, liver, bone, and others outside the pelvis. Currently FIGO staging is used more commonly in the treatment of vaginal cancer.

In the FIGO system, studies officially recommended for clinical staging of a tumor are limited in order to preserve consistent labeling across historical data and low resource settings. These studies include pelvic examination, cystoscopy, proctoscopy, chest radiograph, and intravenous pyelogram. Where advanced imaging techniques such as computed tomographic (CT) scans and magnetic resonance imaging (MRI) are available, many providers extrapolate results from these studies into the clinical staging model. Because of its high resolution and ability to discriminate soft tissue plains, MRI of the pelvis can be a particularly useful adjunct to physical exam for determining the extent of tumor invasion into the bladder, rectum, or parametrial tissues. Taylor et al. correlated MRI findings with clinical outcomes in 25 vaginal cancer patients and concluded that MRI could identify 95 % of primary lesions and accurately predicted clinical stage (Taylor et al. 2007). Primary vaginal lesions appear with low-intermediate intensity on T1- and hyperintensity on T2-weighted images (Taylor et al. 2007) and may be better visualized if the vagina is instilled with gel during the study to separate and distend the vaginal walls. Positron emission tomography (PET) scans have become a standard tool for evaluating local, nodal, and metastatic disease for initial evaluation and surveillance of cervical cancer. Not surprisingly, PET has also been widely adopted for evaluation of vaginal cancers and has been shown to have superior sensitivity compared with standard CT for detecting both primary vaginal tumors (100 % with PET vs. 43 % for CT) and nodal metastasis (Lamoreaux et al. 2005).

8 Screening and Prevention

Similar to other rare cancers, screening for vaginal cancer among low-risk populations is not recommended. The American Cancer Society and American Society for Colposcopy and Cervical Pathology (ASCCP) recommend routine vaginal cytology in women who have had a hysterectomy *only* if there is a history of high-grade cervical dysplasia (CIN2/CIN3) (Saslow et al. 2012). Because VAIN and squamous cell carcinomas are closely associated with HPV infection, HPV vaccination campaigns are likely to be the most important strategy to prevent these diseases.

9 Histologic Subtypes and Management

9.1 Vaginal Intraepithelial Neoplasia (VAIN)

Vaginal intraepithelial neoplasia (VAIN), also known as vaginal carcinoma in situ, is a form of squamous cell atypia that is confined to the squamous epithelium of the vagina, without any evidence of invasion. The characteristics of VAIN include nuclear atypia, loss of squamous cell maturation, and the presence of suprabasilar mitoses. Similar to cervical intraepithelial neoplasia (CIN), VAIN1 involves the deepest 1/3 of the epithelium, VAIN2 the deepest 2/3, and VAIN3 the full thickness of the epithelial layer (Fig. 1). VAIN is almost always associated with HPV infection in more than 90 % of cases, with HPV 16 being the most common subtype, found in up to 65 % of cases of VAIN2/VAIN3 (Smith et al. 2009). The true natural history of VAIN is not known; however, it is considered premalignant because of its association with high-risk HPV types. Invasive squamous cell carcinoma has been identified in up to 12 % of vaginectomies performed for VAIN2/VAIN3 (Indermaur et al. 2005).

Treatment strategies for VAIN include observation, local excision, partial or total vaginectomy, ablation with laser vaporization or

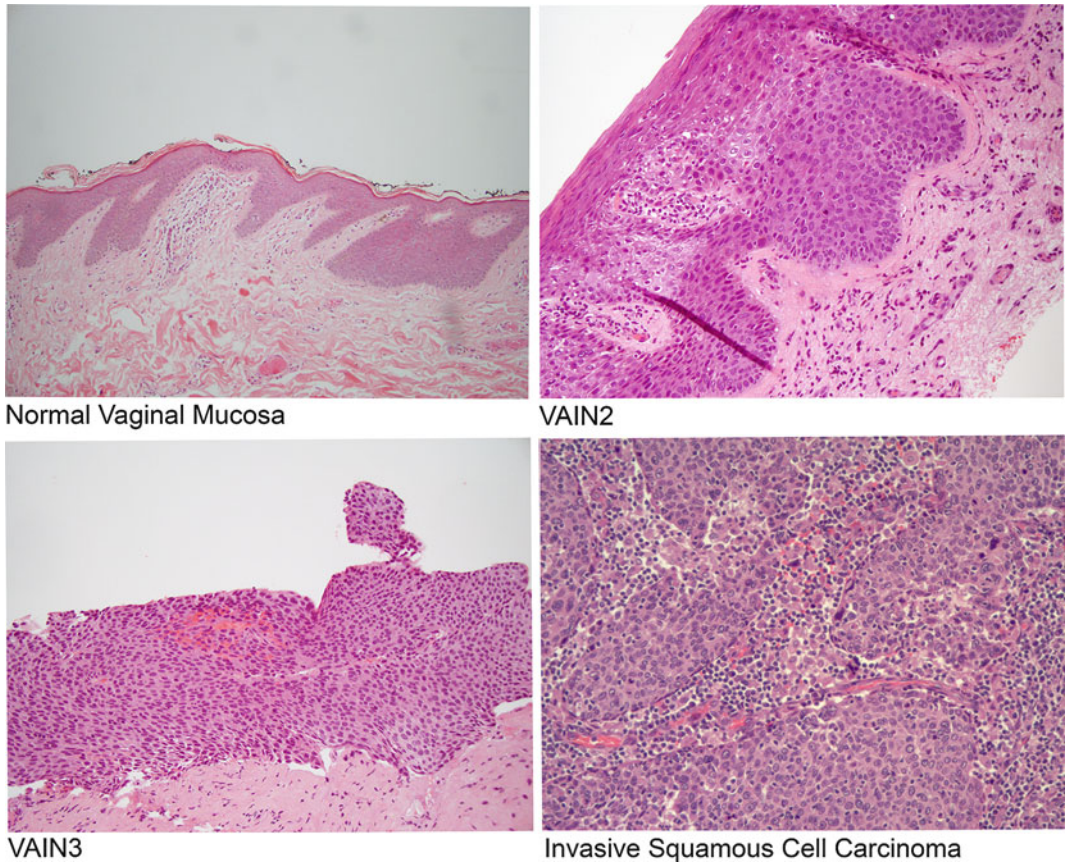

Fig. 1 Vaginal mucosa, high-grade dysplasia, and invasive carcinoma (Ardeshir Hakam 2015)

electrocoagulation, topical 5 % fluorouracil, or intracavitary radiation therapy. Observation is limited to the treatment of VAIN1, which is more likely to regress spontaneously. For VAIN2/VAIN3, published disease control rates are similar for all approaches. Most studies consist of small, single institutional case series, and modalities have not been directly compared for efficacy. The choice of therapy should be individualized based on the size, location, and severity of VAIN lesions, as well as the patient's age, general health and life expectancy, desire for sexual function, and prior history of treatment failures. In a significant subset of women, VAIN is chronically persistent and recurrent and may require repeated treatment with multiple modalities. Risk factors for recurrence include multifocal disease, VAIN3, and older age (Dodge et al. 2001). In all cases, invasive carcinoma should be ruled out with adequate sampling biopsies prior to initiating treatment. Treatment strategies are summarized in Table 2.

Surgical excision is the most appropriate management when invasive carcinoma cannot be ruled out, as this is the only approach that will provide tissue for diagnosis. For patients with a focal, well-circumscribed lesion, local excisional colpectomy is the best choice. In more extensive disease, an upper or total vaginectomy may be necessary to obtain adequate margins. These procedures are usually performed vaginally; however upper vaginectomy may require an abdominal approach in some cases, ideally using minimally invasive technique. Vaginectomy can lead to shortening or stenosis of the vagina and loss of sexual function. Reconstructive procedures and

Table 2 Treatment modalities for vaginal intraepithelial neoplasia

Method of treatment	Applications/advantages	Risks and side effects
Surgical excision	Pathologic diagnosis Evaluate for invasive cancer Total vaginectomy provides definitive treatment	Vaginal shortening or stenosis (large excision) Loss of sexual function (vaginectomy) Possible laparotomy or other surgical complications Generally requires anesthesia
Ablation (CO_2 laser or electrocautery)	Preservation of vaginal length Treatment of multifocal or extensive disease Lower rates of sexual dysfunction	Vaginal stenosis may occur Diagnosis of invasive cancer can be delayed Generally requires anesthesia
5-Fluorouracil	Coverage of diffuse or multifocal disease Does not require anesthesia	Vaginal burning Vaginal ulceration Diagnosis of invasive cancer can be delayed May cause vaginal adenosis in rare cases after CO_2 ablation
Imiquimod	Coverage of diffuse or multifocal disease Does not require anesthesia	Vaginal burning Vaginal ulceration Diagnosis of invasive cancer can be delayed
Vaginal estrogen	May augment other treatment modalities	Unproven as monotherapy
Radiation therapy	Usually definitive Effective when other modalities have failed	Vaginal shortening or stenosis Vaginal fibrosis Sexual dysfunction or loss of function Impaired wound healing Radiation cystitis/proctitis Premature menopause/ovarian ablation

skin grafts may be necessary after total vaginectomy. Women with a prior history of radiation therapy are also at increased risk of surgical complications and fistula formation following colpectomy and vaginectomy procedures.

CO_2 laser vaporization is proposed as relatively noninvasive approach that may be useful for large VAIN lesions and multifocal disease in women who want to retain sexual function. The procedure is generally well tolerated, and patients report minimal sexual dysfunction. Ablation procedures should only be performed if an underlying invasive carcinoma can be adequately ruled out and if the entire lesion can be visualized. Lesions that are partially obscured should be excised.

Topical therapies may be useful for women with low-grade persistent VAIN or diffuse, multifocal disease in women who are poor surgical candidates, after invasive carcinoma has been ruled out. The advantage of these modalities is that the entire vaginal surface can be treated, including difficult to access crevices at the vaginal apex. Proposed topical agents include 5-fluorouracil (5FU), imiquimod, and vaginal estrogen. Of these, **5FU** is the best studied. Several 5FU dose regimens have been proposed, but none have been directly compared, and the most commonly used dose is 2 g once weekly for 10–12 weeks (Gurumurthy and Cruickshank 2012). Side effects of vaginal 5FU include burning and vaginal ulceration. Zinc and other barrier creams may be used to protect unaffected areas, and vaginal estrogen may reduce vaginal discomfort. Vaginal columnar metaplasia (adenosis) has been reported when 5FU is administered after prior CO_2 laser ablation, but the significance of this finding is unknown (Paczos et al. 2010; Gurumurthy and Cruickshank 2012). **Imiquimod**, a topical immune modulator, has also been shown to have activity against VAIN in a few small studies. As with 5FU, dosing regimens vary from series to series. Buck et al. reported that 86 % of a 42-patient series experience regression of VAIN after a 3-week course of once weekly application of 0.25 g 5 %

Table 3 Histologic subtypes of vaginal cancer and their characteristics

	Squamous cell carcinoma	Adenocarcinoma	Melanoma	Rhabdomyosarcoma (sarcoma botryoides)
Epidemiology	Age >60 HPV (HPV 16) History of cervical dysplasia Chronic irritation	Age 14–22 or >60 DES exposure (clear cell) Vaginal adenosis, endometriosis, or mesonephric rests	Age ~60 White, non-Hispanic	Early childhood
Signs/ symptoms	Abnormal pap (ASCUS-HSIL) Vaginal bleeding Vaginal mass	Abnormal pap (AGUS) Vaginal bleeding Vaginal mass	Pigmented lesion Vaginal bleeding Discharge	Grape-like vaginal mass
Treatment modalities	Chemoradiation (EBRT + brachytherapy) Vaginectomy (localized stage I in upper vagina) Pelvic exenteration (central disease)	Conservative surgery Fertility sparing (young patients) Chemoradiation	Surgery Targeted therapies Immunotherapy	Chemotherapy Conservative surgery Radiation
Other histologies: leiomyosarcoma, carcinosarcoma, endometrial stromal sarcoma, yolk sac tumors, neuroendocrine tumor, glassy cell carcinoma, verrucous carcinoma, Wilms tumor, Ewing sarcoma, lymphoma				

HPV human *papillomavirus*, *ASCUS* atypical squamous cells of undetermined significance, *HSIL* high-grade squamous intraepithelial lesion, *AGUS* atypical glandular cells of undetermined significance, *EBRT* external beam radiation therapy

imiquimod cream (Buck and Guth 2003). Side effects of Imiquimod include vaginal burning and irritation. In the Buck et al. series, these side effects were well tolerated, and there were no reports of vaginal ulceration. **Topical estrogen cream** has been advocated as a useful adjunct to all VAIN treatment modalities. Particularly in postmenopausal women with significant vaginal atrophy, topical estrogen therapy may improve detection of VAIN by normalizing adjacent epithelium. Estrogen may also play a role in promoting regression of VAIN (Rhodes et al. 2014).

Radiation therapy is one of the most effective therapies for VAIN, but is less commonly used because of toxicities associated with radiation including vaginal shortening, stenosis, and fibrosis which may interfere with both sexual function and future examinations. Other toxicities include impaired wound healing, risk of inducing premature menopause through ovarian ablation, and radiation cystitis or proctitis. Vaginal intracavitary brachytherapy is most frequently used for definitive treatment of persistent and recurrent VAIN that has failed other modalities, with disease control rates of 86–100 % (Gurumurthy and Cruickshank 2012).

Posttreatment surveillance should be similar to follow up schedules in women with cervical dysplasia: every 6 months for 1–2 years and then annually, with vaginal cytology at each visit. HPV testing has not yet been established in the follow-up of VAIN, but may improve the sensitivity of surveillance exams and allow for improved risk stratification and less frequent follow-up.

9.2 Invasive Squamous Cell Carcinoma

(*Summarized in* Table 3)

Invasive squamous cell carcinoma (SCC) shares cytologic features with VAIN, along with evidence of invasion beyond the epithelial basement membrane. Approximately 65 % of vaginal SCC is HPV positive (Smith et al. 2009). Similar to VAIN, HPV 16 is the most common HPV type found in vaginal cancer, and p16 staining is highly sensitive and specific for HPV infection in vaginal tumors. SCC may be divided into keratinizing and nonkeratinizing subtypes, and other variants including basaloid, warty, and papillary squamotransitional have also been described.

Vaginal SCC is graded by the degree of differentiation. Grade 1 tumors are keratinizing and generally very similar in appearance to squamous epithelium, with abundant cytoplasm. Grade 2 tumors have less cytoplasm, but are easily recognized as squamous cells, whereas grade 3 tumors are both nonkeratinizing and poorly differentiated. Verrucous carcinoma is a distinct type of SCC also found on the cervix and vulva which presents with a large exophytic mass and is generally very well differentiated and cytologically bland appearing. Verrucous carcinoma spreads locally and is generally treated surgical resection.

Treatment strategies for vaginal SCC may include surgery, radiation, or chemotherapy – alone or in combination. Chemoradiation including a combination of external beam and brachytherapy is currently the most recommended treatment modality for vaginal cancer of all stages. Because of the rare incidence of the disease, there are no phase III clinical trials to guide management. Overall, management strategies are based on the results of small case series; extrapolation of treatment strategies for cervical, vulvar, and anal cancers; and expert opinion. Therapy should be individualized for each patient based on the stage of disease, size and location of the tumor, and personal goals for vaginal function. Whenever possible, patients should be referred to tertiary centers to receive care from providers experienced in treating vaginal cancers.

Surgery has limited utility in the treatment of vaginal cancer because of the close proximity of other organs including the bladder and rectum making it nearly impossible to obtain adequate margins with organ-sparing approach, especially when the tumor has invaded beyond the vaginal mucosa. In the 2015 FIGO Cancer Report, Hacker et al. recommend only four situations in which surgery may be useful (Hacker et al. 2015):

1. Patients with stage I disease located in the upper posterior vagina: When a negative tumor margin of at least 1 cm can be obtained, and an adequate pelvic lymph node dissection performed, patients with small stage I tumors may benefit from radical upper vaginectomy (and hysterectomy if the uterus is in situ).
2. Ovarian transposition prior to radiation therapy for young patients. The authors note that debulking of large primary tumors and/or pelvic nodes larger than 2 cm in diameter may be performed at the time of this procedure.
3. Patients with locally advanced, stage IVA tumors may benefit from primary pelvic exenteration, but should also have a pelvic lymphadenectomy and consideration of bilateral groin dissection. This approach may also be combined with preoperative radiation therapy.
4. Patients with a central recurrence following primary radiation therapy should be offered pelvic exenteration if there is no evidence of distant metastases.

Surgical case series report 5-year overall survival rates of 56–90 % for patients with stage I disease treated with partial or total vaginectomy (Davis et al. 1991; Creasman et al. 1998; Ling et al. 2008; Di Donato et al. 2012). Laparoscopic radical vaginectomy with neovagina construction has also been described with excellent overall survival and patient satisfaction. Cancer registry-based studies suggest a survival advantage for patients who are treated surgically when compared with radiation therapy (Ling et al. 2008). Creasman et al. report a 5-year survival rate of 90 % for women with stage I disease in the National Cancer Data Base treated with surgery, compared with 63 % for women who received radiation therapy alone and 79 % for women who received combined surgery and radiation therapy (Creasman et al. 1998). Similarly, Shah et al. also reported a trend toward improved survival in the SEER database for women with stage I disease treated by primary surgery; however, differences in the hazard ratios were only statistically significant when surgery was compared with no treatment for stage I disease (Shah et al. 2009). Trends toward improved survival with surgical management have also been reported for women with stage II disease, but these are not statistically significant, and survival rates are lower overall when compared to women with stage I disease.

In general, improved survival among women treated with primary surgery likely reflects careful selection criteria biased toward women with small, superficial tumors and little comorbidity. The true advantage of primary surgery for patients with early-stage vaginal cancer is preservation of ovarian and sexual function and avoidance of other radiation-related toxicities.

For women with locally advanced disease, anterior, posterior, or total pelvic exenteration is necessary in order to achieve adequate margins around the tumor. Eddy et al. reported 50 % 5-year survival among six patients with stage IVA disease who underwent pelvic exenteration following preoperative radiation (Eddy et al. 1991). In general, exenteration should only be offered to patients who have a reasonable chance of long-term survival after the procedure. Preoperative evaluation should include efforts to rule out pelvic sidewall involvement or nodal and distant metastases. Most surgeons advocate beginning the procedure with exploratory laparotomy and pelvic lymphadenectomy to evaluate for peritoneal or nodal disease prior to beginning the exenteration.

Radiation therapy techniques may include intracavitary or interstitial brachytherapy, external beam radiation therapy (EBRT), or intensity-modulated radiation therapy (IMRT). Practical considerations in the selection of radiation modality, dosing, and technique are summarized in the American Brachytherapy Society consensus guidelines and American College of Radiology Appropriateness Criteria for the management of vaginal cancer (Beriwal et al. 2012; Lee et al. 2013). Because of the high rate of local recurrence and lymph node involvement, most vaginal cancers should be treated with a combination of EBRT and brachytherapy.

Most vaginal cancers are treated with pelvic EBRT to a dose of 45–50.4Gy in 25–28 fractions, followed by a boost to a cumulative dose of approximately 70Gy to the primary tumor site. The clinical target volume includes the gross tumor volume with a 1–2 cm margin, the entire vagina and paravaginal/parametrial tissues out to the pelvic sidewalls, and the bilateral pelvic lymph nodes, which generally correspond to the L5/S1 interspace. For tumors involving the middle or distal 1/3 of the vagina, inguinal nodes should also be included (Yeh et al. 2001). When pelvic lymph nodes are known to be involved, or bulky para-aortic nodes are present on pretreatment imaging studies, extended field coverage of the para-aortic region may be necessary.

The boost to the primary tumor site may be accomplished through brachytherapy or IMRT or a combination. Selection of brachytherapy technique depends on the residual tumor thickness following EBRT. Vaginal cylinder brachytherapy is appropriate for residual disease mainly confined to the mucosa. Tandem and ovoids are typically used for women who have an intact uterus. When the depth of tumor involvement is greater than 5 mm, interstitial implants are required to adequately provide a definitive dose to the entire tumor. Interstitial applicator placement is usually done with epidural anesthesia in order to provide adequate pain control during the procedure and therapy. Laparoscopy or laparotomy may be necessary for appropriate interstitial catheter placement in large tumors in order to prevent inadvertent injury to the bowel. Marker seeds of fiducial gold, platinum, or carbon fiber can be used to define the extent of gross disease. Both low and high dose rate (LDR and HDR) protocols have been reported for the treatment of vaginal cancer, and neither has been definitively shown to be superior. There are fewer studies describing HDR; however, the advantage of this dose schedule is fewer fractions, and rather than continuous radiation dosing requiring radiation precautions, HDR protocols allow for visits and nursing care in between treatments (Beriwal et al. 2012).

Among radiation therapy series of more than ten patients, 5-year disease-specific survival ranges from 36 to 100 % for stage I disease, 31 to 80 % for stage II disease, 8 to 80 % for stage III disease, and 0 to 40 % for stage IV disease (Di Donato et al. 2012). The range of survival rates likely reflects differences in radiation protocol as well as differences in the characteristics of each tumor.

Concurrent chemoradiation therapy has become the standard of care for locally advanced cervical cancer and has been increasingly adopted

as the primary treatment strategy for most vaginal cancers (Lee et al. 2013). In small series, chemotherapeutics including 5FU, mitomycin C, and cisplatin with concurrent radiation therapy resulted in 5-year survival rates of approximately 65 % (Di Donato et al. 2012). Some authors report locoregional recurrence rates as high as 61 % following chemoradiation (Roberts et al. 1991), but these reports are difficult to interpret due to variations in stage and tumor size among studies. In the largest single institution report, Miyamoto et al. present a significantly lower recurrence rate (15 % vs. 45 %, $p = 0.027$) for 20 patients with stage I–IV disease who received chemoradiation (mainly weekly cisplatin) compared with 51 patients who received radiation therapy alone (Miyamoto and Viswanathan 2013). Recently, a large National Cancer Data Base study by Rajagopalan et al. found that 48.6 % of 8086 patients who received radiation also received concurrent chemotherapy. Concurrent chemoradiation therapy was significantly associated with improved 5-year overall survival in all stages and for the entire cohort (48.8 % for chemoradiation vs. 41.9 % for radiation alone). Median overall survival was also significantly increased for all stages of disease when compared with patients who received radiation alone (109 vs. 85 months for stage I, 85.8 vs. 41.7 months for stage II, 43 vs. 19.9 months for stage III, and 18.5 vs. 9 months for stage IV) (Rajagopalan et al. 2014).

Neoadjuvant chemotherapy prior to radical surgery has also been advocated in patients with stage II disease. Panici et al. describe 11 patients who received 3 cycles of cisplatin and paclitaxel followed by radical surgery. In this series, 27 % had a complete response and 64 % had a partial response prior to surgery, and 73 % were disease-free at a median follow-up of 75 months (Panici et al. 2008).

Posttreatment surveillance for vaginal cancer should follow Society of Gynecologic Oncology guidelines (Salani et al. 2011). For high-risk patients (those who were treated with chemotherapy, radiation, or surgery followed by adjuvant therapy or who had advanced disease), a focused history and careful exam should be performed every 3 months for the first 2 years after completing therapy and then every 6 months until 5 years without evidence of disease, after which visits can be repeated annually. Low-risk patients who have stage I disease and were treated by surgery alone may follow up every 6 months for the first 2 years and then annually. Vaginal cytology should be obtained annually to screen for microscopic recurrence, and any cytologic abnormalities should be evaluated with colposcopy. Symptoms such as vaginal bleeding or discharge, pelvic or abdominal pain, new palpable mass, or change in bowel or bladder habits should prompt a CT abdomen pelvis or PET CT to assess for recurrence. There is no evidence to support routine imaging in the absence of symptoms.

Treatment complications affecting vaginal function and the lower urinary and GI tracts are the most common due to the close proximity of vaginal cancers to these pelvic structures. Radiation-related toxicity to the pelvic organs may include radiation cystitis or proctitis and vesicovaginal or rectovaginal fistula. Vesicovaginal and rectovaginal fistulas have also been reported as a complication of radical surgery. Vaginal radiation toxicity includes acute vaginitis, vaginal stricture, vaginal stenosis, or, rarely, vaginal necrosis. In series reporting rates of toxicity, the incidence of grade 2 complications has been reported to be 15–25 % (Gadducci et al. 2015). Factors that increase risk of complications include older age, smoking, medical comorbidities affecting vascular profusion and healing such as diabetes and hypertension, and prior pelvic surgery.

Vaginal stricture and stenosis can be reduced with a combination of topical estrogen cream and dilator use. Women who are sexually active should continue to have intercourse on a regular basis if tolerated. Sexual dysfunction following treatment for vaginal cancer is likely multifactorial, and alterations in body image are common.

Loss of fertility and premature menopause are important considerations in the treatment of young women. We recommend that women of reproductive age be offered consultation with reproductive endocrinology regarding fertility preservation options such as oocyte or embryo cryopreservation prior to initiating therapy for

vaginal cancer. Ovarian transposition to the anterior abdominal wall may reduce the likelihood of radiation-induced menopause and should be considered for some young patients.

Patterns and rates of recurrence vary with initial stage at diagnosis. For stage I disease, the recurrence risk is approximately 10–20 %, compared with 30–40 % for stage II, and 50–70 % for stage III and IV (Davis et al. 1991; Chyle et al. 1996; Perez et al. 1999; Tabata et al. 2002). Among patients with stage I disease, locoregional recurrence is far more common, whereas patients with advanced locoregional disease at the time of diagnosis also have higher rates of both persistent disease and new distant metastases, which may occur in up to 47 % of patient (Perez et al. 1999; Tabata et al. 2002). Recurrent disease portends a very poor prognosis, with a 5-year survival rate of only 12 % (Chyle et al. 1996).

As in the primary setting, salvage treatment strategies include surgical resection, radiation, and chemotherapy. Patients with stage I disease who did not receive radiation initially may be may receive radiation therapy with curative intent. Radiation protocols in this setting are similar to those used at the time of diagnosis and should include EBRT for empiric coverage of pelvic lymph nodes. Recurrences in the distal 1/3 of the vagina should also be treated with empiric sterilization of the bilateral groins. Similarly, in patients with a prior history of radiation, radiation may still be a reasonable option for disease outside the previously radiated field. Patients who have previously received chemoradiation present a therapeutic challenge because bone marrow reserves have been depleted. Women with local recurrence limited to the central pelvis should be offered pelvic exenteration, which offers the only path to long-term disease-free survival, particularly among patients who have failed definitive radiation.

Distant metastases are best treated with systemic chemotherapy, palliative radiation if focal in nature, or best supportive care. Few studies evaluating chemotherapy for recurrent vaginal cancer exist, and most report a poor response to therapy. In a phase II trial presented by Thigpen et al. of the Gynecologic Oncology Group (GOG 26C), only 1/22 women experienced a complete response to cisplatin 50 mg/m^2 given every 3 weeks. Combination therapy appears to be similarly ineffective. In a study of combination of bleomycin, vincristine (Oncovin), mitomycin C, and cisplatin (BOMP), only 1/15 women treated for recurrent disease experienced a response, compared with 5/6 treated in the primary setting (Belinson et al. 1985). For this reason, many patients who are not candidates for exenteration pursue palliative care.

Prognosis has improved with advances in radiation and chemotherapy and particularly with adoption of chemoradiation (Rajagopalan et al. 2014). In a SEER database study by Shah et al. in 2009, stage is the most important predictor of prognosis. A summary of survival rates by stage at diagnosis is provided in Table 1. Other factors linked to shorter overall survival in large cancer registry studies include larger tumor size (>4 cm), lymph node involvement, and older age (Creasman et al. 1998; Shah et al. 2009; Rajagopalan et al. 2014; Gadducci et al. 2015).

9.3 Adenocarcinomas

(*Summarized in* Table 3)

As discussed earlier in this chapter, most vaginal adenocarcinomas reported in the literature are DES-related clear cell carcinomas occurring in adolescents and young women. The prognosis of vaginal clear cell carcinoma is better than for squamous cell carcinoma, with 5-year survival rates of 92 % for stage I and 83 % for stage II disease (Senekjian et al. 1987, 1988). In contrast, non-DES-related vaginal adenocarcinomas carry a relatively poor prognosis. In a series from MD Anderson, the median age at diagnosis was 54 and 5-year survival of only 34 %, compared with 58 % among squamous cell carcinoma patients at the same institution (Frank et al. 2007). Both DES-related and non-DES-related adenocarcinomas are treated similarly to vaginal squamous cell carcinoma. The management of adolescent and young women should include efforts to preserve fertility and sexual function when possible. When a tumor is too large for local excision and

radiation is planned, laparoscopic ovarian transposition should be considered to reduce risk of premature menopause.

9.4 Melanoma

(*Summarized in* Table 3)

Primary vaginal melanoma is the third most common primary malignancy of the vagina, representing 3–6 % of all vaginal cancers (Creasman et al. 1998; Shah et al. 2009) and only approximately 1 % of all melanomas. Vaginal melanomas most often present as a pigmented or ulcerated lesion in the distal 1/3 of the vagina. Amelanotic lesions have also been described and can be mistaken for squamous cell carcinoma. Immunohistochemistry staining for S-100, HMB45, or Melan-A may be helpful in confirming the diagnosis. The average age at diagnosis is approximately 60, and the majority of patients are white non-Hispanic (Leitao et al. 2014).

The prognosis of vaginal melanoma is very poor, with 5-year overall survival of 5–20 % (Creasman et al. 1998; Leitao et al. 2014). Survival for vaginal melanoma is also poor compared to melanomas arising in other sites, likely due to diagnosis at later stages of disease. Melanomas are classically thought to be resistant to radiation, and few traditional systemic chemotherapies have been shown to be active. As a result, surgical resection is the mainstay of therapy for vaginal melanoma, with clear surgical margins being the most important determinant of disease control. Acceptable clinical margins for melanoma are 0.5 cm for melanoma in situ, 1 cm for Breslow thickness less than or equal to 2 mm (AJCC T1 or T2 tumors), and 2 cm for Breslow thickness greater than 2 mm (Garbe et al. 2010). Breslow thickness has not been evaluated for vaginal melanoma, and FIGO staging of vaginal cancer is frequently used. Pelvic exenteration has not demonstrated superior survival compared with wide local excision. Even though sentinel lymph node dissection (SLND) is associated with improved survival in cutaneous melanoma, it has not been widely adopted or evaluated in vaginal melanoma cases. Adjuvant radiation using a similar approach to that used for vaginal squamous cell carcinoma has also been reported, with the possibility of cure. Preoperative radiation can also be considered as a way to improve the chance of complete resection for larger tumors.

Treatment should be approached with consultation with a melanoma specialist at a tertiary center whenever possible. Traditional chemotherapeutics have not been demonstrated to improve overall survival, but there is promising data supporting combination of chemotherapy with targeted agents and immunotherapies. While targeted therapies have not been formally evaluated for primary vaginal melanoma, the BRAF inhibitor vemurafenib and immune modulator ipilimumab have yielded promising results in the melanoma field. In light of recent developments and rapidly improving outcomes using novel agents, women with vaginal melanoma should be encouraged to consider clinical trial participation when such opportunities are available.

9.5 Mesenchymal Tumors

Vaginal leiomyosarcoma, a bulky, rapidly growing smooth muscle tumor with a high mitotic index, is the most common mesenchymal tumor of the vagina in adults, but is extremely rare in general. Radical surgical resection offers the best chance of cure, but 5-year overall survival is only 36 % (Peters et al. 1985). **Vaginal carcinosarcoma and primary vaginal endometrial stromal sarcoma** have also been reported. Treatment of these tumors is generally extrapolated from strategies employed for the corresponding uterine primaries.

Embryonal rhabdomyosarcoma (sarcoma botryoides, summarized in Table 3**)** is characterized by the presence of cross-striated rhabdomyoblasts. This rare tumor has been treated with radical surgery including pelvic exenteration in the past, but is now more commonly treated with chemotherapy in combination with more conservative surgery and radiation. The Intergroup Rhabdomyosarcoma Study Group (IRSG) has conducted four clinical trials from

1972 to 1997, including all tumor sites that are used to guide therapy and is now in the process of a fifth study (Raney et al. 2001). The IRSG classifies tumors into four groups: (I) localized disease that is completely excised with no microscopic residual tumor; (II) complete gross resection of disease with microscopic residual disease, including regional disease with positive lymph nodes; (III) incomplete resection with gross residual disease; and (IV) distant metastases. In the IRS-I through IRS-IV studies, patients in groups I–III received a combination of vincristine, actinomycin D, and cyclophosphamide (VAC) for 12 months sometimes in combinations with ifosfamide, or etoposide, and patients in group IV were randomized to receive vincristine and melphalan (VM) or ifosfamide and doxorubicin (ID) followed by VAC and radiation therapy.

9.6 Other Histologies

Rare variants of vaginal cancer have been reported including primary vaginal lymphoma, Wilms tumor, and Ewing sarcoma, as well as germ cell tumors including childhood vaginal endodermal sinus tumors and variants of epithelial carcinomas such as glassy cell and small cell neuroendocrine carcinomas. Treatment of such variants should be individualized and may include elements of management for vaginal cancer combined with therapies adapted for similar histologies at more common disease sites.

10 Summary

Primary vaginal cancer is a rare entity. Squamous cell carcinoma is the most commonly seen histology affecting women in their sixth and seventh decade of life. Most, but not all, squamous cell carcinomas of the vagina are related to HPV infection. Majority of women are asymptomatic or present with vaginal bleeding or a vaginal mass. The diagnosis and staging are accomplished primarily through physical exam, with confirmatory biopsies, although PET and MRI studies are likely to have an increasing role in predicting prognosis and determining optimal treatment. Radiation is the mainstay of therapy except in select cases of focal, early-stage disease or central recurrences. With the introduction of chemoradiation, overall survival approaches rates seen in cervical cancer. Because of the rarity of this disease, there is no recommended screening; however HPV vaccination efforts hold promise for reducing the incidence of this disease in the future.

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Diagnosis and Management of Vulvar Cancer

Mariko Shindo, Yutaka Ueda, Tadashi Kimura, and Koji Matsuo

Contents

Abstract

Vulvar cancer is rare, comprising only 5 % of all gynecologic malignancies. However, the incidence of invasive vulvar carcinoma has been increasing moderately over the past two decades, and the incidence of in situ vulvar carcinoma has increased more than fourfold in the same period. Vulvar squamous cell carcinoma, the most common form of this cancer, is commonly divided into two basic types: HPV-associated and HPV-independent. To improve vulvar cancer survival, early detection by careful screening is important. FIGO surgical staging system for vulvar cancer was updated in 2009, incorporating prognostic factors such as inguinal lymph node metastasis. The number and morphology including the size, extracapsular spread of the involved nodes have been taken into account. The presence of fixed or ulcerated inguino-femoral nodes is also included to a staging system. The standard treatment for vulvar cancer has been primarily surgery; however, to decrease morbidity and improve survival outcome, more conservative and individualized treatment practices have recently been explored. The benefit of postoperative adjuvant therapy has been shown in the past decades; although an indication for adjuvant therapy needs further discussion. In advanced vulvar cancer, multimodality therapy including neoadjuvant chemoradiotherapy followed by surgical resection and definitive chemoradiotherapy has

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been investigated to avoid exenterative surgery or stoma formation. For patients with clinical positive inguino-femoral lymph nodes, node dissection or neoadjuvant chemoradiation therapy are now recommended.

Keywords
Vulvar cancer • Squamous cell carcinoma • HPV • Conservative therapy • Management

1 Introduction

Vulvar cancer is a relatively rare disease of the female genital tract, accounting for roughly only 5 % of all gynecologic cancers. In 2015, the estimated number of expected new cases of vulvar cancer in the United States alone will be 5,150, with 1,080 accompanying deaths (Siegel et al. 2015). One large retrospective study found that, from the years 1973 to 2000, the incidence of invasive vulvar cancer in women had increased by approximately 20 %, from 1.8 cases per 100,000 to 2.2 cases per 100,000 (Judson et al. 2006), whereas the incidence of in situ carcinoma rose by an alarming 411 %, from 0.56 cases per 100,000 women to 2.86 per 100,000, during the same period. The same study observed that the incidence of invasive vulvar cancer begins to increase quickly after age 50 and that it peaks between the ages of 65–70. Conversely, the incidence of the noninvasive in situ form increases only until roughly the age of 40–49, whereupon it declines

Histologically, vulvar squamous cell carcinoma (SCC) is the most common histologic subtype of vulvar cancer, accounting for 80–90 % of such malignancies (Beller et al. 2006), with vulvar melanoma being the second most common type. Other significant histological types include vulvar basal cell carcinoma, Paget's disease of the vulva, vulvar adenocarcinoma, and Bartholin's gland carcinoma. Vulvar Paget's disease is discussed in the separate chapter.

There are at least three main histological types of vulvar SCC: warty, basaloid, and keratinizing. Rarer histological variants of SCC are verrucous carcinoma, keratoacanthoma-like SCC, sarcomatoid carcinoma, and SCC with giant tumor cells. The warty and basaloid patterns affect younger women, having risk factors similar to cervical cancer, and both are highly associated with high-grade vulvar dysplasia. The keratinizing pattern, which is a dominant pattern consisting 65–80 % of invasive vulvar SCC, affects older women and often accompanies lichen sclerosis or squamous hyperplasia.

In the large study which reports over 1,700 cases of vulvar SCC, 25.1 % were human papilloma virus (HPV) positive. Of all invasive vulvar SCC, 72.2 % was the keratinizing pattern and 19.1 % was the warty and basaloid patterns. The warty and basaloid patterns were more likely to be HPV positive (69.5 %) compared to the keratinizing pattern (11.5 %). HPV type16 was the most common type in invasive vulvar SCC (de Sanjosé et al. 2013).

Two distinct pathways, HPV-associated and non-HPV-associated, were proposed for development of vulvar SCC. In the HPV-associated vulvar SCC, the virus-encoded E6 and E7 oncoproteins cause inactivation of at least two important tumor suppressor proteins, p53 and Rb. In the non-HPV-associated type, it is the direct inactivation of *p53* by missense and deletion mutations that is most frequently identified, although a number of other somatic mutational events are usually present as well.

Because of the rarity of vulvar cancer, most studies have been retrospective clinicopathological reviews. Such studies have shown that the management of vulvar cancer has been making steady progress towards more conservative and individualized treatment plans. The standard treatment for early stage vulvar cancer remains surgery; however, more advanced disease cases are now treated with additional radiation and/or chemotherapy. Unfortunately, the choices of which treatments to use, and when, are still based mostly on case by case.

2 Diagnosis and Staging

The vulva consists of several distinct anatomical structures, the labia majora and minora, clitoris, mons pubis, vaginal vestibule, urinary meatus, and perineum. Over 70 % of vulvar cancers arise

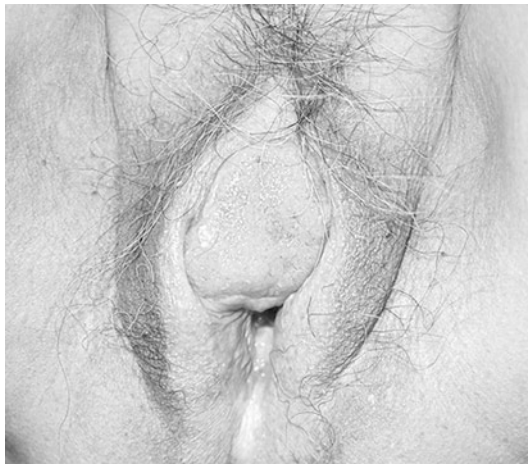


Fig. 1 Squamous cell carcinoma of vulva

in the labia majora and minora. The overt symptoms of vulvar cancer can include pruritus, a palpable mass, a localized pain, vaginal discharge, dysuria, bleeding, or ulceration. However, a significant diagnostic delay for patients with vulvar cancer frequently occurs because the lesion is so often asymptomatic or lacks many of the more alarming symptoms, like unexpected bleeding, associated with other gynecological cancers. This lack of early warning symptoms means that, unfortunately, almost 40 % of patients with vulvar cancer are at advanced stage when first diagnosed (Homesley et al. 1991). Lack of suspicion for vulvar cancer is another reason for delay in diagnosis.

At exam presentation, neoplastic vulvar lesions are usually visible and palpable (Fig. 1). Careful visual evaluation by a physician is important so as not to miss frequently occurring multiple skip lesions. To detect and treat these neoplasms at the earliest possible stages, all suspicious vulvar lesions need to be carefully biopsied. The biopsy will include the surface epithelial lesion and stroma to evaluate depth of lesion invasion, and each lesion needs to be fully histologically assessed. Clinically viable tumor sites but not necrotic areas are recommended for the biopsy site. Along with assessment of the vulva, the groin lymph nodes need to be evaluated carefully. Colposcopy of the cervix and vagina can be performed to detect other squamous intraepithelial neoplasms.

Invasive vulvar cancer usually spreads in two distinct ways: (i) by lymphatic spread to the regional lymph nodes or (ii) by direct expansion into any adjacent structures, such as the vagina, urethra, bladder, rectum, or anal sphincter. Distal hematogenous spread of vulvar cancer is relatively rare.

During lymphatic spread, the first nodal metastasis usually involves the superficial inguinofemoral nodes, and moves subsequently into the deep inguino-femoral and pelvic nodes. Deep inguinal lymph node involvement occurs only in patients with superficial inguinal node metastasis (Andrews et al. 1994). The presence of pelvic lymph node metastasis with an absence of groin nodal metastasis is very rare. Lateral lesions generally drain to the ipsilateral groin nodes. Midline lesions and lesions within 1 cm of the midline can drain to bilateral nodes.

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) committee adopted a surgical staging system for vulvar cancer in which the pathological evaluation of the primary tumor and regional nodes was emphasized, based on the fact that, at the time, metastasis to regional nodes was the most important known prognostic factor and that clinical palpation evaluation of the lymph nodes was known to be unreliable. For example, in one study of 477 patients assessed with vulvar lesions, but having palpably normal groin lymph nodes, 24 % were later found at surgery to have positive nodes (Hoffman et al. 1985; Homesley et al. 1991).

In 1991, problems with the 1988 FIGO surgical staging system for vulvar cancer became more apparent when the Gynecologic Oncology Group (GOG) reported on an analysis of survival outcome of 588 patients. When the patient had both a primary tumor <8 cm in diameter and no nodal metastasis, the 5-year survival was found to be 87 %. This means that lesions up to 8 cm in size are low risk of disease relapse as long as there is no nodal metastasis. Secondly, patients with stage III tumors represented a wide range of survival rates, from 34 % to 100 %. Thirdly, the study found a 5-year survival of 90.9 % for patients with surgically negative nodes, 75.2 % for patients with 1–2 positive nodes, 36.1 % for patients with 3–4 positive nodes, 24.0 % for

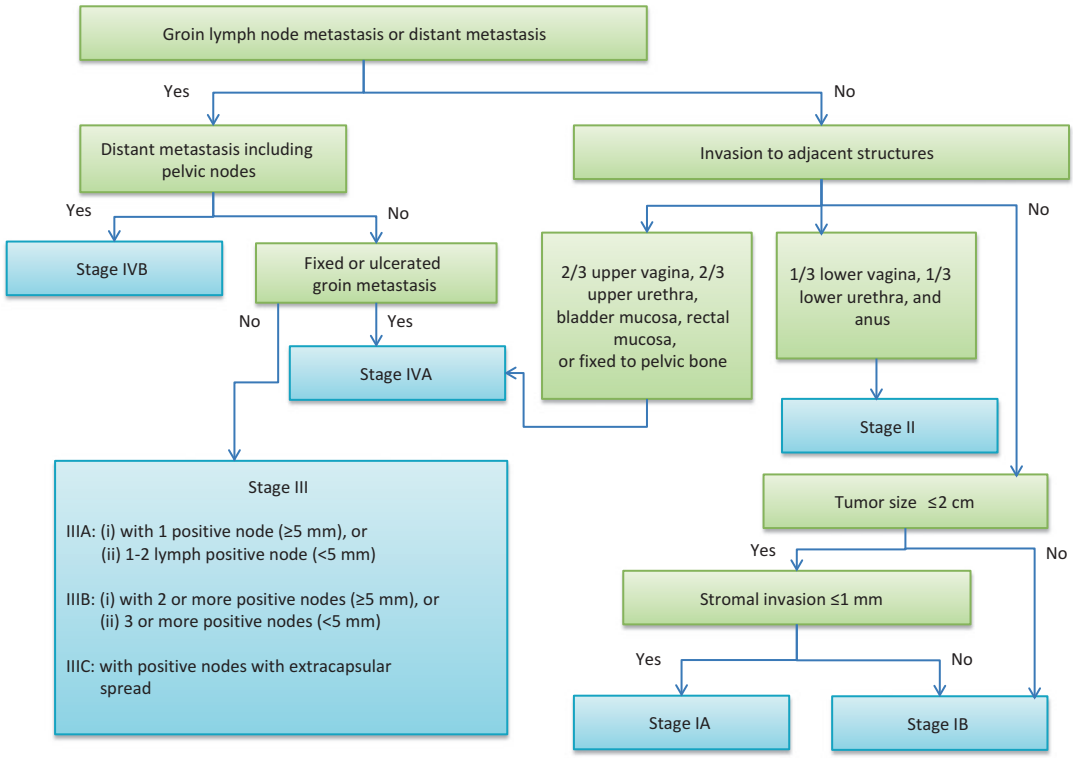


Fig. 2 Staging of vulvar cancer

patients with 5–6 positive nodes, and 0 % for patients with ≥7 positive nodes.

In 2009, after consideration of these problems, FIGO revised the staging for vulvar cancers: Stages I and II in the 1988 classification were combined, and the number and morphology of the involved nodes were now to be taken into account (Pecorelli et al. 2009). Stage IA, the group considered to be at negligible risk of lymph node metastasis, remained unchanged (Fig. 2).

3 Tumor Imaging

There is currently only limited data available on the efficacy of various imaging modalities for the diagnosis and treatment of primary vulvar cancer, although imaging techniques, such as MRI, CT, and PET/CT, currently play important roles in the diagnosis of local, regional, and distal metastasis for treatment planning. This is especially true in advanced vulvar carcinoma, since these patients need more individualized treatment planning, including surgery and chemoradiation, to minimize morbidity.

Kim et al. reported that imaging with MRI was the most accurate modality for evaluation of the primary lesions. To detect lymph nodal metastasis, combined ultrasound imaging and ultrasound-guided aspiration biopsy was found to be the most reliable method, with its high specificity (82–100 %) and sensitivity (80–93 %). The sensitivity of MRI for detecting nodal metastasis was moderate (50–89 %), but the specificity was high (89–100 %).

CT may be an important staging tool for nodal and distant metastasis and for surveillance monitoring after treatment, although CT is less sensitive for detecting a nodal metastasis with size <1 cm because of CT's size criteria (Kim et al. 2013). Cohn et al. showed that the sensitivity of PET/CT is 80 % and the specificity is 90 % for assessment of nodal metastasis (Cohn et al. 2002). However, PET/CT has a limited value in

evaluation of lymph nodes with size <0.5 cm. MRI appears to be the better method for determining the extent and degree of invasion of local lesions, and for detection of small inguinofemoral nodal metastasis, while CT and PET/CT can help detect distant metastasis. PET/CT also plays an important role in the assessment of nodal and distant metastasis, when the clinical diagnosis is difficult.

4 Prognostic Factors

Many studies have retrospectively assessed the prognostic factors that are in play for vulvar cancer. Collectively, they have found that the most significant factor is nodal status. FIGO staging, tumor size, patient age, tumor grade, depth of stromal invasion, and lymphatic capillary space invasion are also predictive for survival probability. In the 26th FIGO Annual Report, involving 1,600 patients with vulvar cancer, the respective 5-year overall survival (OS) rate for each stage was: stage I 78.5 %, stage II 58.8 %, stage III 43.2 %, and stage IV 13.0 %, respectively (Beller et al. 2006).

The previously mentioned GOG study of 588 patients reported that, of all the pathologic findings based on surgery, the status of the inguino-femoral lymph nodes and the tumor diameter were the only significant independent factors for prognosis. In their study, there were 34 % of patients with nodal metastasis. The 5-year survival rate was 91 % in the negative-node patients but only 57 % in the positive-node patients. Histological nodal metastasis was significantly related to clinical node status, lymphatic capillary space involvement, tumor differentiation, patient age, and tumor thickness (Homesley et al. 1993).

5 Treatment of Early Stage Disease

5.1 Surgical Therapy

Historically, the surgery for vulvar cancer was a "classic radical vulvectomy". It required en bloc removal of the entire vulva, including the complete vulvar skin and subcutaneous tissue and the bilateral groin nodes through a butterfly-shaped incision. This procedure achieved an overall survival of around 70 %; however, it could also cause severe complications, including postoperative wound breakdown. Additionally, infection occurred in 50–80 % of these vulvectomy cases, and lymphedema of the lower extremities and psychosexual disturbances were also prevalent. In the past few decades, to decrease surgical morbidities and improve the quality of life of the patient without compromising survival outcome, surgeons have made several modifications to their surgical treatment plans. Contemporarily, the treatment of vulvar cancer is far more individualized. Some of the more important modifications are as follows: an en bloc dissection has been replaced by three separate groin incisions, a unilateral lymphadenectomy is now used for selected lesions, the radical vulvectomy has been replaced by a more localized radical excision, and the pelvic lymphadenectomy has been replaced by radiation therapy of the pelvic nodes (Ansink and van der Velden 2000; Burke et al. 1995; Hacker et al. 1981; Hacker and Van der Velden 1993).

As a result of these modifications, especially the separate groin incisions and the localized radical excision, groin complications such as wound infection and breakdown have decreased dramatically, to as low as 17–22 % compared to previously reported rates. However, significant chronic complications, including lymphedema, still occur in about 30 % of cases.

5.2 Surgical Management of the Primary Tumor

A stage IA vulvar carcinoma is defined as one being ≤2 cm in size and having ≤1 mm of stromal invasion. These microinvasive carcinomas can be treated with a wide local excision, which is a removal of the lesion with a 1–2 cm lateral margin and at least a 1 cm deep surgical margin. It is generally felt that a groin lymphadenectomy is not necessary for stage IA because local recurrence and lymph node metastasis are rare for this type of lesion (Hacker et al. 1984b).

Table 1 Terminology and definition of vulvectomy

Wide local resection	A lesion is excised with 1 cm margin. The depth of excision needs at least 1 cm including the skin and superficial subcutaneous tissues
Simple vulvectomy	Removal of the entire vulva, including the skin and superficial subcutaneous tissues. Usually, performed for benign or premalignant lesion of the vulva that are extensive or multifocal
Radical local excision	Radical excision of the portion of the vulva. The surgical margins should be at least 1 cm. The depth of the dissection is from the skin to the urogenital diaphragm. This terminology is sometimes included in modified radical vulvectomy in the broad sense
Modified radical vulvectomy	Radical excision of the portion of the vulva containing the tumor with approximately a 2 cm margin. This usually implies an intermediate resection between a radical vulvectomy and a radical local excision, where most of vulva is removed. This terminology include radical hemivulvectomy, anterior or posterior radical vulvectomy
Radical hemivulvectomy	Radical excision of unilateral of the vulva. This would not remove midline structures like clitoris, urethra, vagina, perineal body, or anus
Radical vulvectomy	Radical removal of the entire vulva down to the level of the urogenital diaphragm. At least 2 cm margins are needed. When the radical vulvectomy is performed through a separate incision, elliptical outer skin incision is used. The anterior border is on the mons pubis. The lateral incision is made along labiocrural folds. The posterior border is the perineal body. The inner vulvar incision is created circumscribing the urethra and vaginal introitus. The traditional or classic radical vulvectomy mean en bloc removal of bilateral groin nodes and the entire vulva, and intervening skin bridge through butterfly skin incision or longhorn skin incision

For more invasive tumors, but that are still confined to the vulva and have clinically negative nodes, a radical local excision or a modified radical vulvectomy, rather than radical vulvectomy, is indicated to reduce surgical morbidity. A radical local excision includes 1–2 cm of tumor-free margin and the deep surgical margin will be carried down to the inferior fascia of the urogenital diaphragm, which is coplanar with the fascia lata and the fascia over the pubic symphysis. The surgical defect is usually closed without tension. A modified radical vulvectomy is an intermediate resection between a radical vulvectomy and a radical local excision, including a radical hemivulvectomy. A modified vulvectomy is more appropriate for patients with multifocal lesions. Definition of terminology for vulvar surgery is shown in Table 1 (Burke et al. 1995; Heaps et al. 1990; De Hullu et al. 2002; Tantipalakorn et al. 2009).

In a report by Heaps et al., 135 patients with vulvar SCC were treated by primary radical resection. The majority had stage I disease (45.9 %). Approximately one sixth of patients (15.6 %) developed a local vulvar recurrence after the primary radical resection. On examination of formalin-fixed tissue specimens, 67.4 % of the patients had a tumor-free histopathologic margin of $\geq$8 mm, and none of these cases had a local vulvar recurrence. Of the 44 patients that had a margin of $<$8 mm, nearly a half of the patients (48 %) recurred. Taking the 25 % shrinkage of tissue that occurs in formalin fixative into consideration, Heaps et al. have suggested that 10 mm of actual tumor-free surgical margin is needed (Heaps et al. 1990).

De Hullu et al. (2002) reported on a series of 253 patients with T1 and T2 disease, in which 168 patients (66.4 %) underwent classical radical vulvectomy with an en bloc inguino-femoral lymphadenectomy and 85 patients (33.6 %) underwent a revised, less radical, wide local excision with inguino-femoral lymphadenectomy through separate incisions. The overall recurrence rate within 4 years was increased in the less radical treatment group (33.3 %) compared with radical treatment group (19.9 %). In the less radical group, 6.3 % of patients developed fatal recurrences, compared with 1.3 % of patients in the radical group. In the less radical group, approximately a half of patients had histologic tumor-free margins $\leq$8 mm, resulting in 11.3 % of local recurrence rate; whereas in the other half patients, with margins measuring $>$8 mm, there were no

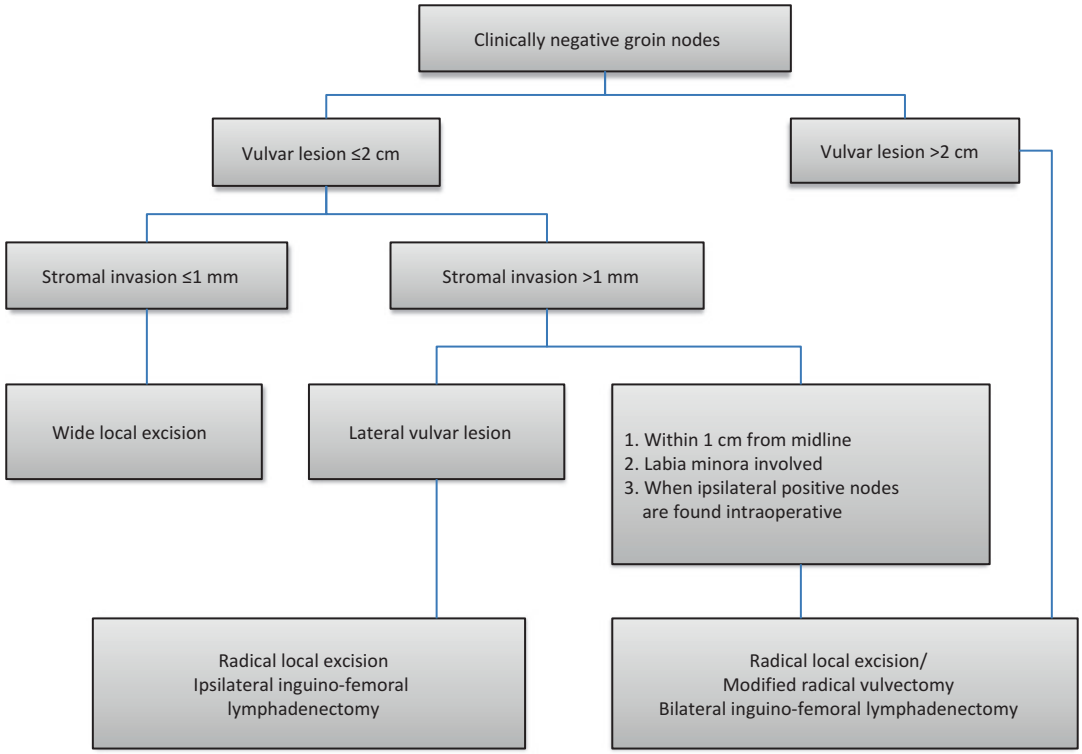


Fig. 3 Management of early vulvar cancer

recurrences. In their study, 50 % of patients had histologic tumor-free margins measuring <8 mm, despite the intended surgical margins of 10 mm. Therefore, the authors recommended obtaining surgical margins of at least 20 mm for the localized surgical treatment of patients with vulvar carcinoma.

A surgical management of early vulvar cancer is shown in Fig. 3.

If a reexcision cannot be performed for patients with a close margin (<8 mm) or a tumor-involved margin, adjuvant radiation therapy may be considered. If the tumor is close to the urethra, the distal 10 mm of the urethra can usually be resected without affecting urinary continence.

5.3 Management of Lymph Nodes

In patients with early stage vulvar disease, with nodes negative by palpation and imaging, metastases to the inguino-femoral lymph nodes are present at surgery in approximately 20–35 % of the cases. Therefore, an appropriate evaluation of nodal status is the most important to decrease vulvar cancer mortality.

The standard procedure for nodal evaluation is a bilateral inguino-femoral lymphadenectomy, which is defined as removal of all the lymph nodes contained in the adipose tissue between the inguinal ligament, the sartorius muscle, and the adductor longus muscle and dissection of the femoral lymph nodes located in the fossa ovalis medial to the femoral vein. To reduce morbidity, a separate groin incision is performed for the vast majority of patients. For selected patients with clinically normal lymph nodes, a more conservative lymph node resection has been suggested. As previously mentioned, the physician can safely omit lymph nodes dissection for stage IA disease. To determine the indication for lymphadenectomy, an excisional biopsy of the

primary lesion at the vulva needs to be performed under local anesthesia to evaluate the stromal invasion.

Ipsilateral groin dissection can be offered to stage IB patients with a unilateral lesion. Some studies have reported that patients diagnosed as having stage I and II vulvar cancer (using the 1988 FIGO standards) can be treated more effectively by ipsilateral inguinal lymphadenectomy. Burke et al. studied 76 patients with T1 and T2 lesions and clinically uninvolved groin nodes, who were treated with radical wide excision and selected inguinal lymphadenectomy. Groin node failure was seen in 5.3 % of the patients; three of the failures were in cases of prior negative dissected ipsilateral groin nodes, only one failure occurred in the undissected contralateral groin nodes (Burke et al. 1995). In a study by Andrews et al., of 84 patients with a lateral T1and T2 vulvar lesion, 56.7 % of the patients were treated with radical vulvectomy with bilateral inguino-femoral lymphadenectomy, and 33.3 % of the patients were treated with radical hemivulvectomy and superficial ipsilateral inguinal lymphadenectomy. No contralateral metastases or recurrences were observed, whereas 10.7 % of patients developed ipsilateral recurrences. The frequency of recurrence was independent of the type of radical surgery performed (Andrews et al. 1994).

The incidence of contralateral node metastasis is <1 % in patients with a unilateral lesion measuring ≤ 2 cm, if the ipsilateral nodes are free of disease (Hacker and Van der Velden 1993). A unilateral lesion is defined as one having the closest tumor margin being >1 cm from the midline structure. Patients with a unilateral tumor measuring >2 cm confined to the vulva (T2 by 1988 FIGO staging) had metastasis to contralateral nodes in 2.4 % (Homesley et al. 1991, 1993).

Under the newer 2009 FIGO classification, the definition of stage II was changed to include a part of the previous stage III. Before determining ipsilateral groin lymphadenectomy to patients diagnosed with stage II disease under the present 2009 FIGO system, it is suggested that a large number of cases need to be further examined. Other risk factors, such as lymphatic capillary space invasion, depth of stromal tumor invasion, and tumor size also need to be considered to better identify a subgroup of patients with lateral T2 tumors who have a low risk of contralateral groin metastasis. Bilateral inguino-femoral node dissection needs to be performed for midline or bilateral tumors, or for those tumors involving the anterior labia minora, and for tumors presenting with any ipsilateral positive nodes.

Conducting only a superficial inguinal lymphadenectomy is correlated with a relatively high rate of groin recurrence, even though the lymphadenectomy-associated morbidity is reduced. Although the groin recurrence rate in patients with no groin nodal involvement at primary surgery is historically <1 %, recent reports indicate that about 4–8 % of patients with negative superficial lymphadenectomy had a recurrence (Burke et al. 1995; Gordinier et al. 2003; Stehman et al. 1992). Because most patients with a groin recurrence of vulvar cancer die, both inguinal and femoral lymphadenectomy are highly recommended. Role of sentinel lymph node in vulvar cancer surgery is discussed in the separate chapter.

5.4 Adjuvant Radiotherapy

Adjuvant postoperative therapy for the primary tumor site can be used when adverse pathologic features are found in the surgical specimen. This includes patients with a positive or close margin (<8 mm), lymphatic capillary space invasion, or a depth of stromal invasion >5 mm, as these characteristics are associated with a higher risk of local recurrence (Heaps et al. 1990).

While it may be a possible approach to include the vulvar tumor site within the radiation field if the tumor express any high-risk factor, current available data remain insufficient to adequately support this concept, especially adjuvant radiotherapy except for close and positive margin and further studies are warranted.

For cases with surgically positive groin nodes, adjuvant irradiation is generally adopted. Pelvic lymphadenectomy alone is no longer preformed for patients with vulvar cancer. One GOG study (Kunos et al. 2009) compared the outcome for

pelvic and groin irradiation after groin dissection with the outcome from solely using pelvic lymphadenectomy. For patients randomized to receive pelvic radiation, the radiation treatment fields encompassed both groins, obturator, and external and internal iliac nodal areas. After a median survival follow-up of 74 months, the relative risk of progression was significantly reduced in the radiation treatment patients (hazard ratio 0.61 $p = 0.02$). At 6 years, overall survival in the radiation patients was 36 %, compared with 13 % for those who received only lymph node dissection. Their data showed a clear benefit for radiation in patients having clinically suspected or fixed ulcerated groin nodes and ≥2 positive nodes. Subsequent studies have emphasized further factors. Patients with one macroscopic metastasis (≥5 mm diameter), extracapsular spread, or ≥2 lymph nodes with micrometastasis (<5 mm) should receive bilateral pelvic and groin irradiation (Hacker et al. 2012).

Recently, in a retrospective multicenter study analyzing over 1,600 patients, the efficacy of adjuvant radiotherapy for node-positive patients was examined. Of all 447 patients (27.9 %) who have groin nodal metastasis, 244 patients (51.1 %) received adjuvant therapy. The majority (84 %) received adjuvant radiotherapy, while 14 % received chemoradiation therapy. Three-year progression-free survival (PFS) rates in these patients were better compared with node-positive patients without adjuvant radiotherapy (40 % vs. 26 %, hazard ratio 0.67, $p = 0.004$), whereas the difference in 3-year overall survival rate was statistically not significant. This study suggest that adjuvant radiotherapy is associated with better outcome in patients with ≥2 positive lymph nodes, although the effects of adjuvant radiotherapy on patients with single lymph node metastasis remains unclear (Mahner et al. 2015).

A medium- or high-energy photon beam (6–18 MV), with anterior-posterior and posterior-anterior fields, is recommended for the standard radiotherapy modality. CT-based planning is essential to determine the depth of the inguinal nodes to be treated. The treatment field should include the inguino-femoral nodes, the obturator nodes, and the external and internal iliac nodes. The cephalad border of the pelvic field needs to extend to the mid sacroiliac or L5/S1 joints. If the patient has suspected or proven internal or external iliac involvement, the cephalad border can be extended to the L3/4 or L4/5 level, so as to include the common iliac nodes. The caudal border needs to cover the vulva or the inferior margin of the tumor; the lateral border extends 2 cm laterally, to the widest point of the pelvic inlet. The suggested treatment fields for adjuvant radiation therapy, where vulvar adverse factors and groin nodal metastasis are integrated, are shown in Table 2 based on our best practice.

Table 2 Suggested radiation field based on tumor factor

Tumor site		Radiation field		
Vulva	Groin node metastasis	Pelvis	Groin	Vulva
High-risk (−)	Negative	No	No	No
High-risk (+)	Negative	No	No	RT if positive margin[a,b]
High-risk (−)	Positive[c]	Yes[d]	Yes[e]	No
High-risk (+)	Positive[c]	Yes[d]	Yes[e]	RT if positive margin[a,b]

Vulvar high-risk factor: close <8 mm or positive margin, large tumor >4 cm, lymphovascular space invasion, stromal invasion >5 mm

[a]Re-resection is another option

[b]Controversy to give RT for other high-risk factors such as close margin, large tumor, LVSI+, and deep stromal invasion

[c]Groin and pelvic radiation is indicated for following factor: one macroscopic micrometastasis (≥5 mm diameter), extracapsular spread, or ≥2 or more lymph nodes with micrometastasis (<5 mm)

[d]Radiate whole pelvis if bilaterally positive or unknown contralateral side in unilaterally positive case; radiate ipsilateral pelvis if unilateral positive after bilateral dissection (Morrow and Curtin 1998)

[e]Bilateral groin radiotherapy is recommended

For treatment of microscopic groin metastases or the primary site, a dose of 50 Gy is recommended. If there are multiple metastases, or an extracapsular extension, the dose is 50–60 Gy. For gross residual disease, the dose

needs to be brought to 60–70 Gy (Halperin et al. 2013).

A midline radiation block can be used to protect the radiosensitive vulvar tissues from the radiation, if there is no indication to treat the vulva itself. However, because of the reported high local recurrence rate found with use of a midline block, its routine use should be avoided (Dursenbey et al. 1994).

The effectiveness of chemoradiation treatments in an adjuvant setting in patients with groin nodal metastasis has not been systematically studied. A few studies, each evaluating fewer than ten patients, have treated patients with a combination of 5-fluorouracil (5-FU) and CDDP or mitomycin C with radiation therapy. The role of adjuvant chemotherapy alone has also not been adequately investigated. Bellati et al. enrolled 14 patients with inguinal node metastases after primary surgery. Cisplatin (100 mg/m^2) was administered at 21 day intervals for four cycles. Four of 14 patients (29 %) had recurrence, including 14 % recurrence rate in the groin, during a median of 57 months of follow-up. The 3-year OS and PFS were 86 % and 71 %, respectively. The author concluded that adjuvant chemotherapy is feasible, with an acceptable complication rate (Bellati et al. 2005). Further studies are necessary to compare these strategies in patients affected by high-risk disease.

The most significant acute complication of radiation alone or chemoradiation therapy is mucocutaneous reactions such as erythema and moist desquamation in the vulva, perineum, and inguinal lesion, which are expected early during the course of the treatment. This skin reactions may require a treatment break depending on degree of reactions, so that skin care is important. Acute hematologic toxicity is common under the setting of chemoradiation therapy. For severe leukocytopenia, colony-stimulating factors may be needed, and severe anemia can be treated with blood transfusions. The late complications include vulvar skin atrophy, telangestasis, dryness of the vaginal mucosa, and vaginal stenosis. When the pelvis is included in the radiation field, acute enteritis may occur during the treatment, and late complications may occur several months to years after the completion of radiotherapy including proctitis and cystitis.

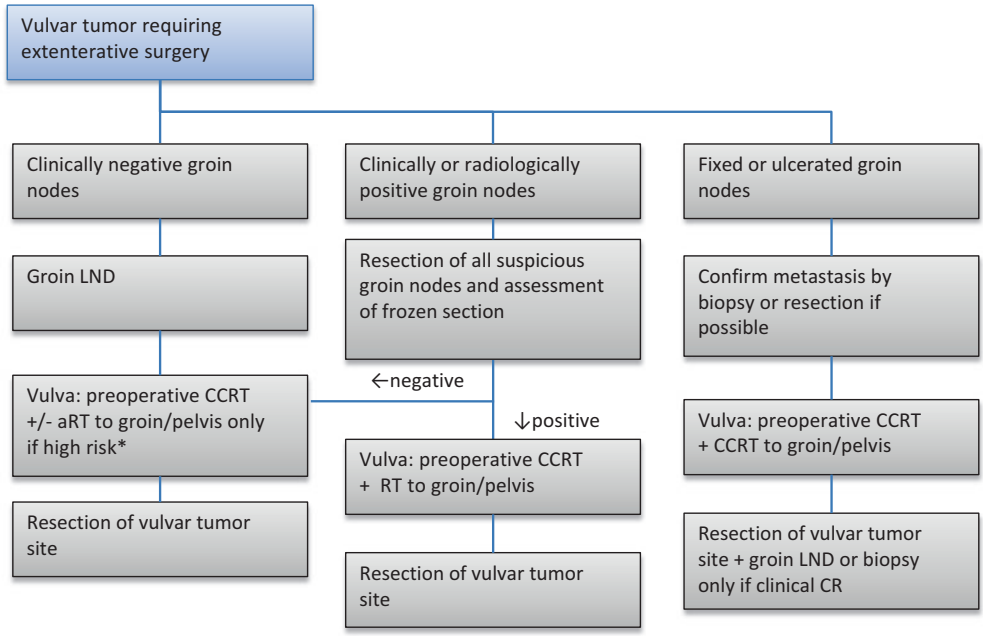
6 Management of Advanced Stage Tumors

6.1 Surgery Advanced Disease

For patients with stage III or IV vulvar cancer, combinations of multimodal treatments are needed. A primary surgical resection is the best option, if the tumor can be resected without a need for a stoma by conducting modified radical vulvectomy or radical vulvectomy. For some patients, with tumors involving the distal urethra, anus, anal sphincter, rectovaginal septum, or rectum, exenterative operations, combined with radical vulvectomy, have been used to achieve an adequate surgical margin. For larger vulvar tumors, plastic reconstruction procedures are considered following an exenterative surgery or radical vulvectomy. However, because an exenterative procedure compromises the quality of life, with significant amounts of physical and psychological morbidity, alternative therapies, such as chemoradiation followed by radical vulvectomy and lymphadenectomy, have been explored to reduce the tumor burden and to allow for a more conservative surgery. If the primary surgical treatment would compromise sphincter function, such that a bowel or urinary stoma would be needed, preoperative chemoradiation is more desirable.

6.2 Management of Groin Lymph Nodal Metastasis

A thorough evaluation of the status of groin nodes needs to be initially performed to plan the overall treatment. When the primary tumor is advanced and needs a stoma formation if proceeds upfront surgical treatment, groin nodal biopsy or node resection, and inguino-femoral lymphadenectomy can be performed first, based on the groin nodal status. So that postoperative groin radiotherapy can be delivered with the radiation for primary tumor at the same time.

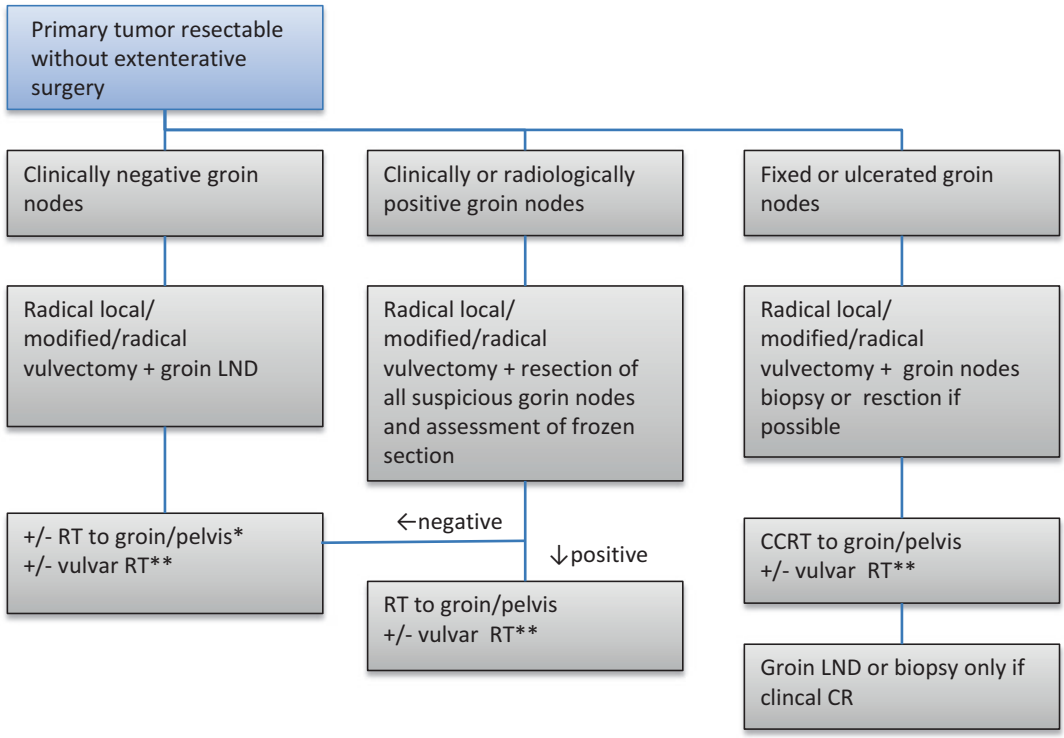


*one macrometastasis (≥5 mm diameter), extracapsular spread, or ≥2 lymph nodes with micrometastasis (<5 mm). LND: lymphadenectomy, RT: radiation thearapy, aRT: adjuvant radiation therapy, CCRT: concurrent chemoradiotherapy, CR: complete response

Fig. 4 Proposed management of advanced vulvar tumor requiring extenterative surgery

If there is a clinically determined high suspicion of inguino-femoral lymph node metastasis, node resection is recommended and a complete inguino-femoral lymphadenectomy is suggested to avoid because a complete groin dissection, together with postoperative groin irradiation, may result in severe lymphedema. Only the palpably enlarged nodes from the groin and pelvis are to be removed. If nodal metastasis is confirmed, the patient should be given postoperative groin and pelvic radiation.

If there are pathologically positive unresectable nodes, as in ulcerative or fixed nodes, after confirming the presence of the pathologically positive nodes by biopsies, preoperative combined chemotherapy and radiation therapy are recommended prior to the groin lymphadenectomy. In one GOG study of patients with vulvar cancer, with what was considered to be unresectable N2/N3 lymph nodes, the patients were first treated with radiotherapy (total 57.6 Gy, 1.7 Gy fraction) and cisplatin combined with 5-FU. Following the chemoradiation, the residual disease in the lymph nodes became resectable in 95 % of the patients, which was combined with surgical resection of the residual tumor. Of those patients who completed the chemoradiation, 88.1 % of the patients received both vulvectomy and lymphadenectomy. In the patients who were treated with chemoradiotherapy, the resulting resected lymph nodes were histologically negative in 41 % of the cases (Montana et al. 2000). By integrating primary tumor and groin nodal metastasis, a suggested management of advanced tumors which otherwise require exenterative surgery including stoma formation if proceeds upfront surgical treatment is shown in Fig. 4, and a management of advanced tumors resectable without stoma formation is shown in Fig. 5.



*one macrometastasis (≥5 mm diameter), extracapsular spread, or ≥2 lymph nodes with micrometastasis (<5 mm)

** if there is positive margin , re-excision or vulvar RT are recommended.

LND: lymphadenectomy, RT: radiation thearapy , aRT: adjuvant radiation therapy, CCRT: concurrent chemoradiotherapy, CR: complete response

Fig. 5 Proposed management of advanced vulvar tumor resectable without extenterative surgery

6.3 Role of Chemoradiation Therapy

The GOG101 trial has studied the effectiveness of cisplatin and 5-fluorouracil (5-FU) as part of the chemoradiation therapy used as a neoadjuvant therapy for patients with locally advanced vulvar cancer, who otherwise would require exenteration to achieve negative surgical margins. Seventy-three patients received 47.6 Gy (1.7 Gy fraction). After chemoradiation, 46.5 % of the patients had no evidence of residual tumor at the time of the planned surgery. Only 2.8 % of these patients still had residual unresectable disease (Moore et al. 1998).

The existing series of retrospective studies regarding the efficacy of chemoradiation have shown a range of complete clinical responses, from 47 % to 90 % (Cunningham et al. 1997; Moore et al. 1998; Tans et al. 2011). To allow better organ preservation, some of these studies describe encouraging evidence for the efficacy of replacing exenterative surgery with primary chemoradiation, forgoing subsequent surgery (Cunningham et al. 1997; Landoni et al. 1996; Moore et al. 1998). In a prospective study by Landoni et al., 58 patients with locally advanced or recurrent vulvar cancer received preoperative radiotherapy (54 Gy) with 5-FU and mitomycin C. The majority (89 %) completed the chemoradiotherapy. Objective responses were observed in 80 % of the vulvar tumors and in 79 % of the cases with groin metastases. Approximately one-fourth (27 %) had a complete clinical response confirmed by vulvar biopsy.

A radiation dose of 45–55 Gy is recommended (Hacker et al. 1984a; Halperin et al. 2013).

Following chemoradiation, to reduce complications when a complete response is achieved, instead of conducting a radical vulvectomy, a surgical biopsy of the vulva can be alternatively performed (Moore et al. 2012). A lymphadenectomy is recommended regardless of whether or not there has been a clinical complete response, because residual disease is often found in the lymph nodes (Montana et al. 2000). For patients unable to tolerate radical vulvectomy, or for those who are deemed unsuitable for surgery because of the site or the extent of the disease, definitive chemoradiation therapy is a treatment choice. A total radiation dose of 60–70 Gy is recommended.

Combined chemotherapeutic agents, such as 5-FU/cisplatin and 5-FU/mitomycin C, are often used for chemoradiation treatment for vulvar cancer. For the treatment of locally advanced vulvar cancer, a recent phase II trial conducted by GOG examined the effectiveness of a radiotherapy (total 57.6 Gy, 1.8 cGy fraction) with weekly cisplatin (40 mg/m^2) followed by surgical resection of the residual tumor (or biopsy to confirm complete clinical response) for the treatment of locally advanced vulvar cancer. Among 58 evaluable patients, there were 69 % of the patients who completed treatment. High rates of complete clinical response (64 %) and histological response (78 %) were demonstrated. In the GOG101 study, the total radiation dose was 47.6 Gy. In this latter study, a 20 % higher dose of radiation, 57.6 Gy, was delivered, in hopes of achieving better results. The treatment-related toxicity of this approach was found to be acceptable. Common adverse effects included leukopenia, pain, radiation dermatitis, pain, or metabolic change. There were four patients who experienced anemia (grade 3–4) and one of these patients received a blood transfusion (Moore et al. 2012).

Recently, intensity-modulated radiation therapy (IMRT) has been suggested be highly beneficial for lowering the incidence of severe toxicity, by reducing the radiation dose to normal tissue. Beriwal et al. presented results from 42 patients treated with IMRT and 5-FU/cisplatin; they showed a high rate of complete pathologic response (48.5 %) (Beriwal et al. 2013). The treatment in this series was well tolerated, with only 2.5 % of the patients requiring hospitalization for intravenous hydration after developing severe diarrhea.

6.4 Role of Chemotherapy

Although attempts have been made to decrease the risks of surgical morbidities and to palliate the symptoms of locally advanced disease, the role of neoadjuvant chemotherapy is still limited in vulvar cancer. There have been only a few studies with single- or combination-agent chemotherapies. The most studied single agent chemotherapy regimen is bleomycin, which has been shown to induce a response rate of between 45 % and 80 % (Aragona et al. 2012; Deppe et al. 1979; Domingues et al. 2010; Tropé et al. 1980). Additional single agents that have been tested in vulvar cancer are cisplatin, paclitaxel, and adriamycin. Table 3 shows a list of examples of combination chemotherapies that have been studied in vulvar cancer (Aragona et al. 2012; Domingues et al. 2010; Durrant et al. 1990; Geisler et al. 2006; Tropé et al. 1980; Wagenaar et al. 2001).

The Gynecological Cancer Cooperative Group of EORTC conducted two different phase II trials with bleomycin, methotrexate, and the alkylating agent lomustine/CCNU (BMC). The overall response rate in the two studies was 56 % and 64 %, and the complete response rate was 8 % and 11 %, respectively. In the latter study, the median progression-free survival was 4.8 months and the median survival was 7.8 months. The 1-year overall survival rate was 32 %. Unfortunately, severe and life-threatening toxicities were documented in both studies. Severe mucositis was observed in 21 % of the patients, and 14 % had a severe infection. Severe pulmonary toxicity was seen in up to 7 % of cases, and there was one death in each of the studies. Hematologic toxicity and nausea/vomiting were also common. These toxicities suggested that the BMC schedule was not well tolerated in the group, consisting of elderly women (Durrant et al. 1990; Wagenaar et al. 2001). Geisler et al. reported using a

Table 3 Combination chemotherapy for advanced/recurrent vulvar cancer (Based on Wagenaar et al. 2001)

Author	Date	Chemotherapy regimen	No. of patients	Complete response (%)	Partial response (%)	Response rate (%)	Postchemotherapy operability rate (%)
Mosher et al.	1973	BM	1	100		100	
Morrow et al.	1973	AP	1				
Vogl et al.	1976	MHO	2				
Guthrie et al.	1978	MOB + VB	3		100	100	
Hakes et al.	1979	MO	2				
Trope et al.	1980	BMc	9	11	44	55	
Belinson et al.	1985	BOMcP	3				
Chambers et al.	1989	BOMcP	2		50	50	
Durrant et al.	1990	BMC	28	10	54	64	29
Shimizu et al.	1990	BOMcP	1	100			
Benedetti-Panici et al.	1993	PBM	21		10	10	90
Behbakht et al.	1996	BIP	1				
Wagenaar et al.	2001	BMC	25	8	48	56	40
Geisler et al.	2006	P + 5-FU	10	10	90	100	90
Domingues et al.	2010	P + 5-FU	10		20	20	20
Aragona et al.	2012	VBPx	6		100	100	83
Aragona et al.	2012	PPx	6		83	83	83
Aragona et al.	2012	PPx + 5-FU	6		83	83	83
Aragona et al.	2012	P + 5-FU	12		83	83	58

Abbreviations used: *A* adriamycin (doxorubicin), *B* bleomycin, *C* CCNU (lomustine), *Cb* carboplatin, *H* hydroxyurea, *I* ifosfamide, *M* methotrexate, *Mc* mitomycin C, *O* vincristine (oncovin), *P* cisplatin, *Px* paclitaxel, *V* vinblastine

combination of cisplatin and 5-FU on ten patients with locally advanced vulvar cancer and showed a 100 % response rate. Interestingly, three patients treated with cisplatin alone in the same study had no response (Geisler et al. 2006). Assessing the efficacy of these single and combination drugs is challenging because these series are based only on small cohorts of cases. Although no particular drug regimen can be recommended at this time, it should be noted that bleomycin, cisplatin, and 5-FU have been shown to have significant activity as key drugs. However, bleomycin has also been associated with severe pulmonary toxicity.

The epidermal growth factor receptor (EGFR) is overexpressed on the cell membrane of invasive vulvar SCC cases, and higher EGFR expression is significantly associated with the depth of stromal tumor invasion and with disease recurrence. The anti-EGFR monoclonal cetuximab has been used successfully to treat some vulvar cancers. Erlotinib, a small-molecule inhibitor of EGFR, has also been evaluated as a targeted therapy for vulvar cancer. Of 41 patients treated with erlotinib in one study, the overall rate of clinical benefit was 67.5 %, with 27.5 % having a partial response and 40.0 % having a stable disease response (Horowitz et al. 2012).

6.5 Recurrence and Prognosis

Groin recurrences occur in 1–10 % of early stage vulvar cancers (Hacker et al. 1981; Homesley et al. 1991; De Hullu et al. 2002; Stehman et al. 1992). Nodal metastasis has been the most important factor in recurrent diseases. Metastasis to groin nodes is diagnosed in approximately 25–35 % of patients undergoing surgery.

The site of vulvar cancer recurrence varies. One multicenter study evaluating cases of primary invasive vulvar SCC focused on the patterns of recurrence and clinical outcomes. Of 502 patients,

37.3 % of the patients developed a recurrence; these were: perineum, 53.4 %; inguinal nodes, 18.7 %; and pelvis, 5.7 %. Recurrence at distant or multiple sites occurred in 7.9 % and 14.2 % of cases, respectively. Isolated perineal recurrences were more common; they developed in 70 % of the stage I patients. Perineal recurrences appeared during the first year after treatment in 39 % of cases; 72 % of inguinal recurrences also appeared during the first year (Maggino et al. 2000).

The site of recurrence further weighs heavily against patient survival. Groin recurrence occurs earlier and is more likely to be fatal. In one GOG study, of 143 patients who received one or more modifications of therapy, approximately one-fourth (25.9 %) of the patients with vulvar cancer had recurrence, and 54.0 % of these patients died of the disease (Stehman et al. 1996). The median interval to recurrence was 35.9 months, and the median survival time after recurrence was 52.4 months. The median time to recurrence in the groin was 7.0 months, and the median survival time after recurrence was only 9.4 months. Most significantly, 91 % of those with a groin recurrence died of the disease.

6.6 Follow-up

As in other cancers, most authors recommend regular follow-up for patients after treatment. Most centers adopt a follow-up schedule of every 3 months for 2 year, every 6 months for 5 years, and every 12 months thereafter. Because the majority of vulvar cancer is HPV-related, all the areas with possible HPV-related cancer also need a careful examination during follow-up period (cervix, vagina, and anus).

6.7 Melanoma of the Vulva

Melanoma is the second most frequent type of vulvar cancer, representing 5–10 % of such cases. Vulvar melanoma arises from melanocytic cells and is usually pigmented. The mean age of the patients is approximately 60 years. For a primary melanoma without metastasis, the most important prognostic factors are tumor thickness, ulcerations, mitotic rate, and depth of invasion. Symptoms are similar to those of vulvar SCC. The most common melanoma symptom is a vulvar mass. Pain, bleeding, and pruritus are also frequent. Most vulvar melanomas will involve either the labia majora or minora, and multiple sites often occur.

In most cases the clinical appearance of the melanoma varies by subtype. There are four basic histologic types: (i) the superficial spreading melanoma, (ii) the mucosal lentiginous melanoma, (iii) the nodular melanoma, and (iv) acral lentiginous melanoma. Dermoscopy should be used for the differential diagnosis of pigmented lesions. Not only pigmented lesions but also nonpigmented lesions should be examined carefully because there is a unique and rare variant of melanoma which is called amelanotic melanoma. Amelanotic melanoma is difficult to differentiate from other epithelial and nonepithelial malignant tumor due to absence of melanin pigmentation. Adding to the clinical diagnosis, a histopathologic diagnosis for any suspicious lesions is also needed, and the specimen must be examined by dermatopathologists experienced in melanoma. If an excisional biopsy is possible, an incisional biopsy is usually avoided as the latter may lead to misdiagnosis. Immunohistochemical stains, such as S-100, HMB45, or Melan-A, can be helpful, if the histologic diagnosis is unclear.

Melanoma staging is defined by the American Joint Commission on Cancer (AJCC) TNM classification system. Historically, some microstaging systems have been used, including the Clark system (based on the depth of invasion) and Breslow system (tumor thickness) for staging cutaneous melanomas. Currently, Breslow's depth is included as a major prognostic factor in the AJCC staging guidelines for melanoma.

The primary treatment of vulvar melanoma is surgical excision. A wide local excision of the primary lesion, with a negative safety margin, is recommended. Radical vulvectomy is not necessary for most cases. The recommended minimal margin for melanoma is 1 cm for a lesion with $\leq$2 mm thickness, and 2 cm margins are needed for a lesion with $>$2 mm thickness. Although

limited, there is data to suggest that a more radical excision results in lower local recurrence and better survival. As for cutaneous melanomas with clinically negative nodes, elective node dissection has not been shown to have any therapeutic advantage, and sentinel lymph node mapping is now considered the standard approach. Most studies do not indicate a survival advantage for adjuvant therapy for vulvar melanoma. In advanced cases, an individualized treatment plan should be considered (Garbe et al. 2010; Leitao et al. 2014). Melanoma often metastasizes systematically resulting in poor prognosis in such metastatic disease. Recently, targeting programmed death-1 pathway is found to be effective in melanoma. In a large phase III trial presented at European Society for Medical Oncology in 2014, nivolumab showed a higher rate of objective response than chemotherapy (32 % vs. 11 %) in patients with ipilumamab-refractory melanoma (Gunturi and McDermott 2015). Further development is expected in vulvar melanoma.

6.8 Vulvar Cancer in Pregnancy

Vulvar cancer diagnosed during pregnancy is extremely rare. Matsuo et al. conducted a systematic review of the literature to evaluate managements and feto-maternal outcomes of vulvar cancer during pregnancy (Matsuo et al. 2014). In their study, 32 cases were analyzed. The mean age was 30.7; the most common presenting symptom was vulvar mass/swelling (75.0 %). Vulvectomy and inguino-femoral lymphadenectomy were performed in 97.1 % and 63.9 % of the cases, respectively. Cesarean delivery was performed in 46.2 % of the cases. Live birth and full-term delivery rates were 96.3 % and 74.0 %, respectively. Vulvectomy, with the fetus in situ, was performed in 42.4 % cases, and it did not increase the risk of preterm delivery or stillbirth.

The authors pointed out a frequent significant delay of diagnosis in these cases, leading to decreasing both the disease-free survival and overall survival rates. A biopsy of the vulvar lesion, observed at the time of initial presentation for pregnancy care, was conducted in only 46.7 % of the cases. Among the 53 % of biopsy-delayed cases, the mean duration of the delay was 12.8 weeks and the majority (62.5 %) had a delay for more than 8 weeks. Sixty percent of patients who had a delay that exceeded 8 weeks were initially staged at a more advanced stage, compared to 15 % of the patients who had less than 8 weeks of delay. The 5-year disease-free rate was 0 % for the cases with >8 weeks delay in diagnosis compared to 69.1 % for the cases with ≤ 8 weeks delay in diagnosis. The majority (70 %) of delays in biopsy were due to the observed lesions having a low suspicion for malignancy, mainly because vulvar cancer is predominantly considered a disease of postmenopausal women.

Similarly, in the general population there is also often described a delay in the diagnosis of vulvar cancer, which is usually attributed to both the patient and the physician. Patients often hesitate to tell their physician about their vulvar symptoms, and, because it is so rare, physicians may not always recognize the risk for vulvar malignancy. For early diagnosis, an active approach, including a biopsy for suspicious lesions, even during pregnancy, is strongly recommended.

7 Conclusion

For decades we have been making advances in the treatment of vulvar cancer. Investigators and clinicians are now exploring more individualized treatments and multimodal approaches for it. However, we are greatly hampered in developing new clinical trials because of the relative rarity of this disease. Further studies will help us better understand how to integrate chemoradiation, neoadjuvant chemotherapy, sentinel lymph node sampling, and newer approaches, including IMRT and gene-targeted therapy, into our management of vulvar cancer, helping us to decrease its morbidities and improve its treatment outcome for our patients.

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Preinvasive Epithelial Disease of the Vulvar

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Abstract

Premalignant diseases of the vulva include disorders of epithelial growth and differentiation in the vulva. According to the latest classification from the International Society for the Study of Vulvar Disease, the three main categories for intraepithelial neoplasia include vulvar intraepithelial neoplasia (VIN), Paget's disease, and melanoma in situ (MIS). VIN is further divided into the two main categories: The most common one is VIN usual type or HPV related, and the second one is VIN differentiated type. The rate of progression of untreated high-grade VIN to invasive vulvar cancer is ranging from 9 % to 18.5 %. The diagnosis is usually carried out by visual inspection and biopsy is necessary for histologic confirmation. There is no useful screening test available for preinvasive vulvar disease, which highlights the importance of healthcare provider awareness for different existing premalignant vulvar lesions. Surgical excision remains the mainstay of the treatment for preinvasive epithelial vulvar disease. Alternative treatment options for VIN and Paget's disease include ablation and pharmacological treatment. Preinvasive epithelial vulvar disease can recur which warrants long-term patient monitoring. This review highlights epidemiological characteristics, histological patterns, clinical features, diagnostic studies, and management strategies for preinvasive vulvar diseases.

Keywords

Vulvar intraepithelial neoplasia • Paget's disease • Melanoma in situ

1 Vulvar Intraepithelial Disease

Vulvar cancer is the fourth most common gynecologic cancer and encompasses 5 % of all gynecologic malignancies. Some cases of vulvar cancer develop slowly through precancerous epithelial changes in the vulva, which highlights the importance of early diagnosis and treatment of these lesions. In 1966, Jeffcoate assigned chronic vulvar dystrophy to the entire group of disorders effecting vulvar epithelial growth and differentiation. In 1989 the International Society for the Study of Vulvar Disease (ISSVD) replaced the old dystrophy by a new classification shown in Table 1 and includes four different categories. This chapter is a review of third category including VIN, Paget's disease and MIS.

2 Squamous Vulvar Intraepithelial Neoplasia

2.1 Introduction

Vulvar intraepithelial neoplasia (VIN) refers to proliferation of atypical basal cells in the vulvar epithelium and characterized by disordered maturation and nuclear abnormalities. The incidence of VIN has increased fourfold between 1973 and 2000 (ACOG 2011). The mean age at diagnosis is 43 years, and women younger than 50 years old account for 75 % of cases (Jones et al. 2005; Judson et al. 2006).

2.2 Classification

The ISSVD classification in 1986 was based on cellular immaturity, nuclear abnormalities, and

Table 1 Classification for epithelial vulvar disease from International Society for Study of Vulvar Disease (ISSVD)

I. Nonneoplastic epithelial disorders of the skin and mucosa (low malignant potential)
a. Lichen sclerosus
b. Squamous hyperplasia
c. Other dermatoses
II. Mixed nonneoplastic and neoplastic epithelial disorders
III. Intraepithelial neoplasia
a. Squamous intraepithelial neoplasia (VIN 1, VIN 2, and VIN 3)
b. Non-squamous intraepithelial neoplasia
i. Paget's disease
ii. Tumors of melanocytes
IV. Invasive tumors

Table 2 Summary of vulvar intraepithelial neoplasm

	Usual VIN (uVIN)	Differentiated VIN (dVIN)
Age	Young	Postmenopausal
Clinical features	Multifocal, multicentric[a], sharply defined, mostly elevated and involving labia minor	Less specific, mostly unicentric, hyperkeratotic plaques, treatment-resistant plaques
HPV infection	85 %, predominantly HPV 16, 18, or 33	Rare
Risk factors	HPV, cigarette smoking, and immunosuppression	Lichen sclerosus
Pathogenesis	Deregulation of HPV E6-E7 oncoprotein causes suppression of p53, pRB, p21 which leads to inhibition of apoptosis and genomic instability	PTEN mutation, microsatellite instability, gene hypermethylation, p53 inhibition
Prevalence	>96 %	<2–5 %

[a]Multicentric disease means involving the cervix, vagina, anus, or vulva. It is age related, as it decreases from 59 % in women aged 20–34 to 10 % in women over 50 years of age

mitotic activity and defined to three grades, similar to the three-grade cervical intraepithelial neoplasia. In VIN 1, the basal one-third of the epithelium is involved, whereas in VIN 3 the whole thickness of the epithelium is involved. However, ISSVD modified this stance in 2004. The term VIN1 has been eliminated and flat lesions associated with koilocytic changes are consider condyloma, whereas VIN 2 and 3 have been combined and simply referred to as VIN.

ISSVD new classification (2004) (Sideri et al. 2005):

- **VIN usual type (uVIN)** is the most common, with three subtypes including warty, basaloid, and mixed VIN. These lesions are commonly associated with HPV infection.
- **VIN differentiated type (dVIN)** is more often associated with vulvar dermatoses, such as Lichen sclerosus and oncogenic HPV infection is uncommon.
- **VIN unclassified type (VIN NOS)** are rare Pagetoid lesions.

Clinical and molecular characteristics of usual and differentiated VIN are listed in Table 2.

2.3 Clinical Features

VIN can be asymptomatic and noted incidentally during gynecologic examination or may present with a mixed variety of symptoms such as pruritus, pain, vulvar soreness, discharge, bleeding, dyspareunia, or palpable lesions. Vulvar lesions can be any shade from white to red. If pigmented, coloration ranges from pale tan to black, depending on the degree of keratinization, patient race, and the type of lesion. They are usually on non-hair-bearing areas, sharply defined, and can be identified by unassisted vision.

2.4 Risk Factors for VIN

- **Usual type**: HPV, smoking, and immunosuppression
- **Differentiated type**: Lichen sclerosis (Conley et al. 2002)

2.5 Evaluation

- **History:** Medical history needs to be evaluated for risk factors associated with VIN. History of sexually transmitted infections, HPV infection, genital warts, and abnormal Pap test should be obtained.
- **Physical Exam:** The gynecologic examination requires complete exposure and includes inspection and palpation of the entire vulva, groin, and perianal area. The most common locations for VIN lesions are the labia minora and introitus between the positions 3 o'clock and 9 o'clock. Site, size, number of lesions,

shape, color, and degree of thickness need to be reported. Lesions of particular concern include areas with marked hyperkeratosis which are elevated, roughened, nodular, or with an ulcerated surface. Sites most likely to harbor invasive disease are the posterior perineal and perianal areas.

Diagnostic Study: Management is based on histologic diagnosis, and biopsy is indicated for any suspicious lesion. Adequate biopsies can be obtained by using local anesthetic and a punch biopsy up to 6 mm.

- **Colposcopy:** Colposcopy can identify subclinical lesions and the extent of the lesion and detect other synchronous intraepithelial lesions. Evaluation of suspicious areas includes application of 3–5 % acetic acid-soaked gauze pads to the vulva for 5 min (Barbara et al. 2008).
- **HPV detection:** Diagnosis of HPV infection with the VIN lesion is useful to differentiate uVIN from dVIN (koilocytosis, p16 and p53).
- It is mandatory to perform a careful examination of the entire lower anogenital tract, which also includes the cervix and vagina. Performing Pap smear is highly recommended.

Screening for VIN: No screening strategies have been developed for early detection of VIN. When HPV-related VIN is diagnosed in young sexually active women, full evaluation of sexually transmitted infections is recommended.

2.6 Management

Treatment is recommended for all women with VIN. As previously mentioned VIN1 has been eliminated in the new classification and lesions reported as VIN1 may be reassessed annually (ACOG 2011). The goal is to relieve patient symptoms, preserve vulvar anatomy and function, exclude concurrent invasive disease, and prevent progression to invasive cancer. Treatment strategies are based on either destroying affected cells or enhancing the host immune system's response and are selected based on patient and lesion characteristics as well as clinician expertise. Management options include surgery, ablative therapy, and pharmacological therapy.

2.7 Surgery

The mainstay of treatment for VIN remains surgical excision. For high-risk uVIN such as ulcerative lesions, dVIN, history of vulvar carcinoma, and in patients with immunosuppression, surgical excision is required. Preoperative counseling regarding expected anatomical changes especially after extensive surgeries and sexual function is necessary. Special attention has to be paid to the psychosexual consequences and the quality of life of the patients. Surgical modalities include wide local excision, simple vulvectomy, and skinning vulvectomy.

- **Wide local excision (WLE):** WLE is the preferred initial intervention for women where clinical or pathologic findings suggest cancer. WLE is defined as excision of an individual lesion with 0.5–1 cm margin and can be performed with a knife, electrosurgery, or laser CO2 excision (Hart 2001). The margin may be altered to avoid injury to the clitoris, urethra, and anus. The resection depth is also important, in pilous areas, atypical cells can compromise skin appendages, and ideally the whole pilosebaceous complex needs to be resected (recommended resection up to 4 mm). In hairless areas, the resection depth does not need to extend more than 1 mm.

  Loop electrosurgical excision (LEEP) is another modality to perform WLE. LEEP is accomplished with the blend cutting mode, power output of 16 and 30 W using 0.2 mm microneedle, and 1 × 0.4 cm semicircle shape loop. Fulguration requires a 5 mm ball electrode or a 1 mm needle electrode (Terzakis et al. 2010). After finishing the procedure, the area needs to be carefully examined via colposcopy to rule out residual lesions.

CO_2 laser excision is the other available option to perform WLE. The procedure is performed under colposcopic guidance, and the depth of tissue destruction is guided by colposcopy. Laser excision should be performed according to the Reid criteria (Reid et al. 1985). The laser device is set to continuous mode with power density ranging between 750 and 1250 w/cm. An excision is made at the periphery of the lesion in the third surgical plane; then, with the smallest sized laser spot, another excision should be made along the third surgical plane of the entire lesion, with up to 1 mm depth in hair-free epithelium to 3 mm depth in hairy areas to ablate the hair follicle. This requires special training as deep laser excision can lead to destruction of the skin appendage and hypertrophic scar formation. Consequently, large lesions over hair-bearing areas may be preferentially treated with other modalities.

- **Skinning Vulvectomy:** Skinning vulvectomy is a wide superficial vulvectomy, removing the skin and underlying structures while leaving the subcutaneous fat in place, and is rarely needed. It is indicated in confluent multifocal lesions or in patients for whom prior procedures have failed to control the disease.

2.8 Prognosis

Negative margins reduce the risk of recurrence at the same site and warrant the histologic evaluation of specimen margins with frozen sections intraoperatively (Barbara 2008; Jones et al. 2005). The recurrence rate of VIN after excision ranges from 20 % to 40 % (Hillemanns et al. 2006; Jones et al. 2005). In a recent study, the recurrence rate after vulvectomy, partial vulvectomy, local excision, laser ablation, and coagulation was 19, 18, 22, 23, and 56 %, respectively (Van Seters et al. 2005). With regard to LEEP, studies are limited and have reported a recurrence rate between 13 % and 20 %. According to these studies, LEEP and cold knife excision are equivalent in their ability to achieve complete response (Ferenczy et al. 1994; Terzakis et al. 2010).

2.9 Ablative Therapy

Ablation therapy provides a cosmetically appealing treatment with a cure rate comparable to surgical excision but has the disadvantage of not providing a specimen for pathological analysis. It includes laser vaporization and ultrasonic surgical aspiration. It is essential to rule out the coexistence of invasive carcinoma by performing colposcopically directed biopsies.

- **CO_2 Laser vaporization:** Laser CO_2 vaporization combines the advantages of surgical excision in relation to cure rate with correct diagnosis and the advantages of laser vaporization with respect to cosmetic and functional results. A drawback of laser CO_2 vaporization is that there is no surgical specimen for histological evaluation. The procedure is performed under local or general anesthesia, and the laser device is on continuous mode with power density ranging between 750 and 1250 w/cm (ACOG 2011). Vaporization is usually carried out using a defocalized beam, 1–2 mm in diameter with the depth between 1–3 mm. The complete response rate for laser vaporization is almost 75 % (Hillemanns et al. 2006; Jones et al. 2005).
- **Ultrasonic surgical aspiration (CUSA):** This technique uses ultrasound to cause cavitation and disruption of the tissues, which are then aspirated through a tube and collected as a specimen (Barbara et al. 2008). After detailed colposcopy, CUSA is used with a 20° angle hand piece, frequency 23 kHZ, aspiration up to 24 Hg, and irrigation up to 50 cc/min. The hand piece is used similar to a pencil. Recurrence rates up to 35 % have been reported in studies (Miller 2002). The recent Cochrane study comparing CO_2 laser ablation and CUSA reported no significant difference in the recurrence rate (Kaushik et al. 2014).

2.10 Medical Treatment

As with ablative therapy, careful colposcopic examination is warranted to exclude invasive cancer. To date no medication is approved by US Food and Drug Administration for VIN treatment; however, several agents have been studied.

- **Imiquimod:** Imiquimod is an immune response modifier, which enhances cell-mediated immunity and was initially approved for genital condyloma acuminatum. Imiquimod used either alone or in conjunction with other therapies has been subjected to randomized clinical trials with promising results. Imiquimod elicits a strong antitumoral response by activating toll-like receptor on monocytes and dendritic cells. Activated dendritic cells release cytokines such as INFα, TNFα, and IL-12, which induce and activate CD8(+) T cells.

  Recommended regimens include topical application of a thin layer of imiquimod 5 % cream to individual lesions that then remain uncovered overnight – 2–3 nights per week for a total of 12–20 weeks. Colposcopic assessments need to be performed at 4–6-week intervals during treatment. Side effects are common and include erythema, erosion, edema, and pain. A Cochrane review of four trials, comparing imiquimod to placebo, reported that the imiquimod arm achieved better results with either complete response (RR: 11.95) or significant reduction in size and histologic grade of residual lesion (RR: 9.10) in high-grade VIN (Pepas et al. 2015).
- **Cidofovir**: Cidofovir is a cytidine nucleotide analogue with in vitro and in vivo activity against HPV. A thin layer of 1 % cidofovir is applied on the lesion with a gloved finger and then washed off 6–8 h later. The treatment can be applied 3 times a week for maximum 24 weeks. Evaluation is usually performed every 6 weeks after starting treatment. A recent clinical trial of cidofovir compared with imiquimod reported complete response in up to 46 % of patients in the cidofovir group compared to 42 % in the imiquimod group with high-grade VIN (Tristram and Fiander 2005).
- **Photodynamic therapy (PDT)**: PDT is based on light-induced oxidation reactions which lead to necrosis. A systemic or topical photosensitizing compound, usually 5-aminolevulinic acid (ALA), is used and is followed by the application of nonthermal light. Usually wavelength is matched to the absorption characteristics of the photosensitizer. The interaction generates oxygen radicals with high local cytotoxic effects. ALA gel or a patch is spread over the entire vulva, and then the vulva is covered by a nonadherent dressing. Mean time between drug application and light illumination is 3–6 h, and then the gel is washed off with saline. The fluorescence of ALA-induced protoporphyrin is evaluated with wood lamps, and PDT is performed with a non-laser light source. Studies have shown a treatment response rate between 40 % and 70 % (Fehr et al. 2001) with a recurrence rate around 48 % (Hillemanns et al. 2006). Additional trials and long-term studies are required to evaluate the efficacy of this method.
- **Therapeutic HPV vaccines**: The therapeutic effect of HPV vaccines has been reported recently. Vaccines can enhance T-cell-mediated immunity in uVIN lesions. Most vaccines elicit a specific immunity against HPV E6 and E7 proteins (Preti et al. 2015). In a recent study, after injection of quadrivalent vaccine, up to 35 % reduction in subsequent HPV-related disease was reported in patients diagnosed with genital warts, VIN, or VAIN (Joura et al. 2012). In another study, women with HPV-16-positive high-grade VIN were vaccinated with a mix of synthetic long peptides from HPV-16 viral oncoproteins E6 and E7, and complete response in up to 79 % of cases has been reported after 12 months, and this effect was maintained for up to 24 months (Kenter et al. 2009). In a randomized clinical trial, imiquimod therapy followed by three injections of quadrivalent vaccine for VIN showed complete regression in up to 63 % of cases in addition to a significant increase in the number of CD4

and CD8 T-cell counts in lesion responders (Daayana et al. 2010).

2.11 Follow-up

Recurrence of VIN occurs in 30–50 % of cases (ACOG 2011). The true rate of progression with untreated high-grade lesions is not clear, ranging from 9 % to 18.5 % (Jones et al. 2005; Van Seters et al. 2005), whereas progression risk after treatment varied between 2 % and 5 % (Jones et al. 2005; Van Seters et al. 2005). In the majority of studies, follow-up has been limited; therefore, long-term surveillance is necessary. The risk factors for recurrence include multifocal or multicentric disease, high-risk HPV infection, positive margins after excision, immunosuppressant use, HIV, and smoking (Hillemanns et al. 2006; Wallbillich et al. 2012). The general follow-up schema is to repeat the exam at 3–4-month intervals during the first year, then every 6 months during the second and third years, and annually thereafter (Barakat et al. 2002). A recent American College of Obstetricians and Gynecologists (ACOG) committee suggested that women with complete response and no new lesions noted at follow-up are suggested to have a visit at 6 and 12 months after treatment and need to be monitored annually thereafter (ACOG 2011). Treatment for recurrent disease should be individualized and depends on the previous treatment method, location, and risk of occult disease.

2.12 Special Considerations

Pregnancy: Data about VIN in pregnancy is extremely rare. Any suspicious lesion warrants biopsy. If invasive carcinoma is ruled out, expectant management in the third trimester can be considered. Local excision and ablative therapy are available options for patients who are not close to delivery, and they follow the same principles as nonpregnant women (Tseng et al. 2012). Podofilox and sinecatechins should not be used during pregnancy. Imiquimod appears to pose low risk but is recommended to be avoided until more data are available. Management recommendations for pregnancy complicated by invasive vulvar cancer are discussed in the chapter for invasive vulvar cancer.

Immunocompromised: HIV-mediated immunosuppression can result in exacerbation of HPV infection and impairment of the local immunity of lower genital tract (Conley et al. 2002). Therefore, this population has an increased risk for lower genitalia preinvasive and invasive neoplasia. Clinical manifestations are the same as for women without HIV infection, but lesions may be more extensive. A detailed pelvic examination needs to be performed at least once per year, and any suspicious lesions need to be biopsied. There are no established treatment guidelines; however, surgery is the mainstay of therapy. Medical treatment is the second option. There are a few studies reporting promising results using imiquimod and cidofovir for VIN treatment in HIV-infected women (Tristram et al. 2014), and according to a recent study, HAART was associated with a one-third decrease in the incidence of VIN (Massad et al. 2004).

2.13 Prevention

The uVIN shows over 85 % HPV positivity, with type 16 DNA being detected in 75 % of high-grade VIN cases (de Sanjose et al. 2013; Preti et al. 2015). It has been demonstrated that immunization with quadrivalent vaccine will decrease the risk of VIN. The bivalent HPV vaccine is not approved for this indication, as this endpoint was not assessed in clinical trials (ACOG 2011).

2.14 Conclusion

The incidence of VIN is increasing in the past decades. There are two different types of VIN with distinct clinical features, etiology, pathology, and malignant potential. dVIN accounts for a smaller proportion of cases but has a higher risk of progression to malignancy, and surgical excision is the preferred treatment modality. uVIN occurs mostly in younger women, and HPV

infection is the most important risk factor. Due to the low risk of malignant transformation in uVIN, conservative management is recommended. Due to high recurrence rates after treatment, long-term follow-up is crucial. HPV vaccination can potentially prevent and reduce the incidence of uVIN and related invasive vulvar cancer.

3 Vulvar Paget's Disease

3.1 Introduction

Extramammary Paget's disease (EMPD) is a rare noninvasive intraepithelial adenocarcinoma affecting areas rich in apocrine sweat glands. Whereas Paget's disease occurs most often in nipples, EMPD is prevalent to the vulva and accounts for up to 60 % of EMPD and 1 % of vulvar neoplasm cases (Parker et al. 2000). The origin of vulvar Paget's cell remains controversial. It may be viewed as a carcinoma of adnexal stem cells, as a sweat gland carcinoma arising from the intraepidermal portion of the gland, or as a carcinoma derived from the Toker cells of mammary-like glands of the vulva (Regauer 2006). Vulvar EMPD is mostly an intraepithelial lesion but has the potential to invade to the dermal layer. Up to 4–17 % of vulvar EMPD are associated with underlying carcinoma of the vulva. In addition, in 11–20 % of cases, other malignancies involving the vagina, uterus, cervix, breast, bladder, rectum, colon, and gallbladder have been reported (Karam and Dorigo 2012).

3.2 Classification

According to Wilkinson and Brown, vulvar Paget's disease can be subdivided into primary (cutaneous) and secondary. Primary vulvar Paget's disease is an intraepithelial adenocarcinoma arising within the epidermis, while the secondary is defined as involvement of vulvar skin by a noncutaneous internal neoplasm, either by direct extension or epidermotropic metastases (Wilkinson and Brown 2002):

Primary

- Paget's disease as a primary intraepithelial Paget's disease
- Paget's disease as an intraepithelial neoplasm with invasion
- Paget's disease as manifestation of an underlying primary adenocarcinoma of a skin appendage or a subcutaneous vulvar gland

Secondary

- Paget's disease secondary to anal or rectal adenocarcinoma
- Paget's disease secondary to urothelial neoplasm (PUN)
- PUN as a manifestation of intraepithelial urothelial neoplasia
- PUN as manifestation of urothelial carcinoma
- Paget's disease secondary to adenocarcinomas or related tumors of other sites

3.3 Clinical Features

Vulvar Paget's disease is common to postmenopausal Caucasian women. It can be asymptomatic or present with an erythematous, eczematoid, or pruriginous lesion. Many patients are treated for presumed eczema for years prior to a definitive diagnosis (Terlou et al. 2010). Vulvar Paget's disease is characterized by a multicentric nature and usually extends microscopically. Due to the occult fashion of spread beyond the margins, it has a chronic and relapsing course and is difficult to achieve complete elimination of disease. Nearly 10–20 % of vulvar Paget's disease cases are associated with coexisting malignancies at other sites such as the breast, rectum, genitourinary tract, cervix, and skin (Parker et al. 2000; Tebes et al. 2002). Once vulvar Paget's disease is diagnosed, an underlying cancer needs to be ruled out in both vulva and other related areas such as the breast.

3.4 Evaluation

History: Patients with persistent pruritic eczematous lesions that fail to resolve within 6 weeks of

appropriate treatment need to undergo further evaluation. This is important because diagnosis is frequently delayed and may result in the expansion of disease (Tebes et al. 2002).

Diagnostic Study: Diagnosis is based upon the characteristic histopathology. Vulvar biopsy needs to be performed in patients with suspicious lesions. Histologically, vulvar Paget's disease is characterized by the presence of Paget's cells, identified by typical pale vacuolated cytoplasm, high-grade nuclei, and prominent nucleoli. The differential diagnosis includes both benign etiologies such as leukoplakia, condyloma acuminata, contact dermatitis, psoriasis, lichen planus, and malignant conditions such as melanoma, basal cell, or squamous cell carcinoma (Hendi et al. 2004, Wilkinson and Brown 2002). Sometimes immunohistochemistry is required to exclude the differential diagnosis of melanoma and VIN. Paget's cells can express CA125 and Her-2/neu but do not express estrogen receptors (Lu and Chen 2014).

3.5 Management

An outline of various treatment modalities for vulvar Paget's disease is summarized in Table 3.

3.6 Surgery

Surgical resection remains the mainstay treatment of vulvar Paget's disease. Surgical interventions include wide local excision, Mohs micrographic surgery, and vulvectomy.

- **Wide local excision (WLE):** WLE is defined as an excision of the affected lesion to the depth of to 4–6 mm to include the pilosebaceous glands and skin adnexal structure. Margins up to 2 cm are preferred.
- **Mohs micrographic surgery (MMS):** MMS is a specialized surgical resection technique of skin tumors with highly accurate intraoperative mapping and histological assessment of the entire margin at the time of surgery. It allows maximal preservation of normal tissue (Hendi et al. 2004).
- **Vulvectomy (simple or radical)**: Vulvectomy is an invasive management that may be required in cases of concurrent

Table 3 Summary of management for vulvar Paget's disease

Treatment	Study size	Response rate	Recurrent rate	Side effect
Surgical resection[a]	40.5 (22–529)	33–70 %	22–61 %	Graft sloughing, dyspareunia Introital stenosis Sexual disorders
Radiotherapy	17 (2–92)	62–100 %	0–35 %	Acute reaction: radiation cystitis, nausea and vomiting, erythema, irritation, dermatitis Chronic reaction: bladder dysfunction, skin reactions (soreness, ulceration), chronic diarrhea, malabsorption, fistula
Chemotherapy				
Systemic[b]	3 (1–7)	33–50 %	50 %	Myelosuppression, neutropenia
Topical	1 (1–7)	57 %	25 %	Severe local pain, moist desquamation, allergic reaction
Photodynamic therapy	24 (16–32)	14–50 %	38–56 %	Photosensitivity reaction
CO_2 laser ablation	6 (1–6)	33 %	67 %	Severe local pain
Imiquimod	21 (10–31)	52–80 %	19 %	Skin irritation, erosion, pain, ulceration

[a]Surgical resection including wide local resection, vulvectomy (simple or radical), and Mohs micrographic surgery
[b]Systemic chemotherapy for metastatic or invasive vulvar Paget's disease. Sample size: (median, range)

adenocarcinoma or deep invasion of EMPD. It often requires vulvar reconstructive surgery. Vulvectomy with skin graft placement has a 6.8 % risk of having postoperative complications including physical or sexual dysfunction (Lavoue et al. 2013).

3.7 Prognosis of Surgical Resection

Response rates following surgical resection ranged from 33 % to 70 % (Edey et al. 2013; Lavoue et al. 2013; Parker et al. 2000; Tebes et al. 2002). The high recurrence rate is an important consideration for monitoring after surgical management. In a recent study of 529 cases, the recurrence rate after surgery was as high as 58 % (Edey et al. 2013). Positive surgical margins were an important risk factor for recurrence. Patients with negative margins experienced rates of local recurrence between 18 % and 38 % (Edey et al. 2013; Lavoue et al. 2013) in comparison to 46–61 % in patients with positive surgical margins (Edey et al. 2013; Lavoue et al. 2013).

3.8 Medical Treatment

Medical treatment is indicated if patient is not a candidate for surgical resection due to comorbidity or patient choice. Medical treatment can be also recommended for recurrent vulvar Paget's disease after multiple surgical resections.

- **Imiquimod**: Imiquimod is an immune response modifier, which enhances cell-mediated immunity. See the VIN section for the mechanism of action of imiquimod. It is a promising treatment modality especially for patients with recurrence and multiple surgical resections or in patients who are poor surgical candidates. In a small series, response rates of up to 52–80 % have been reported. The recurrence rate is 6.5–19 % regardless of primary versus recurrent disease status (Luyten et al. 2014). In a systematic review of 63 cases, complete response rates of 9.8 %, 31.1 %, and 71.6 % were reported after 2, 4, and 6 months of imiquimod therapy (Machida et al. 2015). Based on this, a 6-month treatment course is suggested for vulvar Paget's disease.
- **Photodynamic therapy**: PDT is a technique using a tumor-localizing photoreactive drug such as 5-aminolevulinic acid with appropriate wavelengths to eliminate tumor cells. Response rates for PDT in vulvar Paget's disease range from 14 % to 50 %, and recurrence rates are 38–56 % (Shieh et al. 2002). Photosensitivity reaction and burning sensation were reported as adverse effects for PDT.

3.9 Alternative Therapy

- **CO_2 laser ablation:** Laser ablation therapy has an advantage of preserving vulvar anatomy. However, the high recurrence rate of up to 67 % is an important concern in vulvar Paget's disease. Laser ablation only penetrates the surface of the skin, and there is a high chance of leaving residual disease, especially in cases of deep dissemination (Louis-Sylvestre et al. 2001).
- **Radiotherapy**: Radiotherapy is an effective treatment in localized vulvar Paget's disease. The downside of radiotherapy is the dose limitation of radiation due to the concern for long-term side effects. Therefore, repeated irradiation to the vulva must be very limited. The response rate ranges from 62 % to 100 %, with a recurrence rate of 0–35 % (Karam and Dorigo 2012; Oashi et al. 2014).
- **Systemic chemotherapy:** Systemic chemotherapy is indicated for disseminated metastatic Paget's disease. No standard chemotherapy guideline has been established. There are numerous case reports describing systemic chemotherapy for metastatic or invasive Paget's disease. Suggested chemotherapy regimens consist of epirubicin with mitomycin C, vincristine, carboplatin, and fluorouracil, mitomycin C plus etoposide and cisplatin, etoposide alone, cisplatin plus fluorouracil, or S1 plus carboplatin. The complete response rate is 33–50 %, with partial response in up to 55–67 % (Matsushita

et al. 2011; Niikura et al. 2006; Oashi et al. 2014).

- **Topical chemotherapy**: Topical chemotherapy with fluorouracil or bleomycin monotherapy has been reported as an alternative treatment for local disease. Various adverse effects including severe pain, moist desquamation, and allergic reaction have been reported. According to studies, response rates are between 57 % and 100 % with a 25 % recurrence rate (Del Castillo et al. 2000).

3.10 Follow-Up for Vulvar Paget's Disease

The overall recurrence rate after standard treatment modalities is up to 30 %. (Luyten et al. 2014). Long-term follow-up is recommended, not only because of the high recurrence rate but also the higher risk of developing a secondary malignancy, which may occur many years after the initial diagnosis. According to a recent population-based study examining 1,439 patients with invasive EMPD that included 781 cases of vulvar Paget's diseases, 80.4 % of cases were limited to local disease with a 5-year disease-free survival up to 94.9 %. However, a significant increase in the rates of secondary vulvar or vaginal malignancy has been reported (Karam and Dorigo 2012). Despite the importance of long-term monitoring in vulvar EMPD cases, no established follow-up guidelines exist to date.

3.11 Conclusion

Vulvar Paget's disease is a rare noninvasive intraepithelial disease, which has a multifocal nature. Standard treatment for vulvar Paget's disease is surgical excision; however, positive margins with residual lesions are common. Because relapse occurs in over 30 % of patients, medical treatment, especially imiquimod, can be an alternative treatment option in the management of vulvar Paget's disease.

4 Melanoma In Situ of the Vulva

4.1 Introduction

Vulvar melanoma is the second most common vulvar malignancy, and due to the poor prognosis, it is an important women's health issue. Vulvar melanoma represents 3.4 % to 10 % of vulvar neoplasms. Melanoma in situ (MIS) is the precursor of vulvar Melanoma which is confined to the epidermis and adnexal epithelium (Kingston et al. 2004). Despite the slow nature of MIS, progression to invasive melanoma is definite (Terlou et al. 2010). Vulvo-vaginal melanoma appears to be biologically different from cutaneous melanoma and is more similar to mucosal melanoma. Pathologically, mucosal melanoma of female genital tract is subdivided into epithelioid, mixed spindle and epithelioid, and pure spindle. Up to 40 % of mucosal melanomas of female genital tract are accompanied with MIS. Breslow thickness is the most significant prognostic factor of outcome in vulvar melanoma (Gru et al. 2014). Management of melanoma of the vulva is described in the chapter for vulvar cancer.

4.2 Clinical Features

Melanoma in situ appears as a pigmented vulvar lesion. Our understanding of MIS natural history is limited, and pure in situ lesions are seldom recognized. The ABCDE scheme (**a**symmetry, **b**order irregularities, **c**olor variation, **d**iameter >6 mm, **e**nlargement or **e**volution of color change) needs to be considered for any pigmented lesions. In situ lesions appear to have good prognosis if completely excised.

4.3 Evaluation

History: Any change in size, shape, or color of the vulvar lesion is important. Personal or family history of dysplastic nevus syndrome is highly important. Exposure to excessive ultraviolet light can be considered as a risk factor for lesions

arising on outer, non-hair-bearing portion of labia major.

Diagnostic study: Punch biopsy is the preferred method because assessing the depth of stromal invasion is important. The most significant histologic prognostic factors for vulvar melanoma are tumor thickness and depth of invasion. The biopsy needs to be performed from the thickest lesion (ACOG 2008). Small lesions can be completely excised. If melanoma is suspected, an excisional biopsy with 1–2 mm margin is necessary. On histologic examination, the in situ component is characterized by atypical melanocytes distributed predominantly along the dermoepidermal junction.

4.4 Management

Surgical resection is the standard approach for MIS. Studies support excision with 5 mm margins as the recommended surgical approach. Destruction by cryosurgery, laser, or cautery is contraindicated (Terlou et al. 2010).

4.5 Conclusion

When vulvar MIS is suspected in a vulvar lesion with changes in the ABCDE scheme, complete resection of a hyperpigmented vulvar lesion is recommended.

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Diagnosis and Management of Gestational Trophoblastic Disease

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Contents

Abstract

Gestational trophoblastic disease (GTD) refers to all tumors that arise from the maternal placenta. Gestational trophoblastic neoplasm (GTN) is a subset of GTD and refers to choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. Persistent GTD may develop after treatment of a molar pregnancy and is also referred to as GTN. The treatment of GTN is stratified based on whether the patient is low risk or high risk as determined by the World Health Organization (WHO) score and International Federation of Gynecology and Obstetrics (FIGO) staging system. Low-risk GTN is treated with single-agent chemotherapy, whereas high-risk GTN should be treated with combination regimens. GTN that does not respond to first-line treatment is said to be resistant or refractory. Resistance to a particular chemotherapeutic regimen is evidenced by a plateau or rise in beta-hCG levels. The overall prognosis for GTN is excellent, even in the setting of refractory disease. GTN affects women of reproductive age, and comprehensive counseling must be performed prior to initiation of gonadotoxic treatment. This chapter also discusses the management of GTN with special considerations such as brain and vaginal metastasis, role of secondary curettage, and post-molar prophylactic chemotherapy.

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1 Introduction

Gestational trophoblastic disease (GTD) is the general term used to describe growth disturbances of the placental trophoblast. GTD encompasses the complete mole, partial mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Gestational trophoblastic neoplasia (GTN) is a subset of GTD and refers to the latter four. The term persistent GTD is often used interchangeably with GTN when referring to the diagnosis of post-hydatidiform mole trophoblastic neoplasia. Typically, GTN will arise after a molar pregnancy but can occur in the setting of a normal pregnancy and in rare cases may not be associated with pregnancy. With the advent of various chemotherapeutic regimens, the prognosis for GTN is excellent.

1.1 Epidemiology

The overall incidence of GTD and GTN is low within the general population. The incidence varies widely based on geographical location and race. Southeast Asia and Japan have the highest incidence of GTD. It is unknown at this time why various ethnicities have a higher incidence of GTD and GTN. Currently, the incidence of GTD is documented at 1–3 per 1000 pregnancies (Froeling and Seckl 2014). Given that GTN typically arises from GTD, the incidence of GTN is much lower. In North America the incidence is quoted to be 1 in 40,000 and at 9 per 40,000 in Southeast Asia and Japan (Lurain 2010).

1.2 Presentation

The presentation of GTN is diverse and dependent on the type of neoplasm. Benign moles such as the complete hydatidiform mole present most often with vaginal bleeding and significantly elevated beta-hCG. The elevation in beta-hCG often correlates to the burden of trophoblastic disease (Froeling and Seckl 2014). A single elevated beta-hCG should not be used to make the diagnosis of GTD or GTN. When an ultrasound is performed, hydropic villi are observed, and this is often referred to as a snowstorm appearance (Froeling and Seckl 2014).

Following evacuation of GTD, beta-hCG levels should steadily decline. The majority of patients will have normal beta-hCG levels around 12–14 weeks after evacuation. A plateauing or increase of the beta-hCG is concerning for the development of GTN or persistent GTD. Regression curves have been developed to help identify patients at risk (Schlaerth et al. 1981). Persistent GTD develops when molar tissue invades into the myometrium. Typically, this is seen with the invasive mole but can also be seen in choriocarcinoma, PSTT, and ETT. Table 1 describes the criteria for the diagnosis of post-hydatidiform mole trophoblastic neoplasia or GTN (Committee 2002). GTN can be diagnosed if any one of the criteria is established.

Histologically, the invasive mole appears as excessive growth of the trophoblastic tissue

Table 1 Criteria for the diagnosis of post-hydatidiform mole trophoblastic neoplasia

GTN may be diagnosed when the plateau of beta-hCG lasts for four measurements over a period of 3 weeks or longer, that is, days 1, 7, 14, and 21[a]
GTN may be diagnosed when there is a rise of beta-hCG of three weekly consecutive measurements or longer, over at least a period of 2 weeks or more, days 1, 7, and 14[a]
GTN is diagnosed when the beta-hCG level remains elevated for 6 months or more

Adopted and modified from FIGO committee report on FIGO staging for gestational trophoblastic neoplasia 2000 (Committee 2002)

[a]A difference of 10% or less between measurements is considered stable and should not be interpreted as a change

Table 2 Summary of clinical presentation and histopathologic findings

GTN type	Presentation /behavior	Histopathology	Management
Invasive mole	• Presents with irregular bleeding after dilation and curettage • Associated with localized invasion; however 15% metastasize to the lung or vagina • High levels of beta-hCG	• Molar tissue which invades the myometrium. • Growth of trophoblastic tissue with the presence of chorionic villi invading myometrium	Chemotherapy
Choriocarcinoma	• Associated with irregular bleeding after dilation and curettage • 50% arise from hydatidiform moles • Increased risk of hemorrhage and vaginal bleeding • Highly malignant tumor with propensity for widespread metastasis via vascular channels- spreading to the lung, liver, and brain • High levels of beta-hCG	• Sheets of anaplastic cytotrophoblasts and syncytiotrophoblasts with absence of chorionic villi	Chemotherapy
Placental Site Trophoblastic Tumor (PSTT)	• Rare • Presents with non-specific vaginal bleeding • Chemoresistant, persistent low levels beta-hCG • Presence of human placental lactogen (hPL) • Metastasizes via lymphatics	• Intermediate trophoblastic tissue without chorionic villi seen invading into the myometrium	Hysterectomy +/− Chemotherapy
Epithelioid Trophoblastic Tumor (ETT)	• Rare • Majority occur after term pregnancy • Presents with non-specific vaginal bleeding • Chemoresistant • Elevated beta-hCG but usually less than 2500	• Mononucleate trophoblastic cells arranged in cords associated with eosinophilic, fibrillary and necrotic debris	Hysterectomy +/− Chemotherapy

Adopted and modified from Lurain (2010)

which invades into the myometrium of the uterus. Invasive moles often have local invasion and are less often associated with metastasis. Choriocarcinoma is a highly malignant tumor associated with hemorrhage, widespread metastasis, and sheets of anaplastic cytotrophoblasts and syncytiotrophoblasts. Choriocarcinomas are typically very chemosensitive. Placental site trophoblastic tumor is a rare form of GTN that arises after a term pregnancy and histologically consists of intermediate trophoblasts. PSTT has slow growth within the uterus and only metastasizes late in its course. Patients with PSTT usually present with low levels of beta-hCG and irregular vaginal bleeding. Surgery of the primary tumor and multi-agent chemotherapy are the mainstays of treatment for PSTT (Lurain 1990); (Abrão et al. 2008; Papadopoulos et al. 2002). Epithelioid trophoblastic tumor is an extremely rare type of GTN with little documentation in the literature. ETT can arise from either a previously gestation or without a previously documented gestation. ETT is chemoresistant; therefore, surgery is the mainstay of treatment when confined to the uterus. Histologically, ETT develops from the chorionic-type intermediate trophoblast (Allison et al. 2006; Lurain 1990) (Table 2).

1.3 Treatment Overview

The treatment for GTN is determined by whether the patient is found to be low risk or high risk. There are two classification systems for GTN: International Federation of Gynecology and

Obstetrics (FIGO) and the World Health Organization (WHO). The FIGO staging criteria defines stage based on extent of disease (Table 3). The World Health Organization (WHO) proposed a classification system that divides patients into low-risk and high-risk categories with the purpose of defining the best course of treatment (Table 4). It uses independent prognostic factors to risk stratify patients based on the likelihood of being successfully treated with single-agent versus multi-agent chemotherapy. Low-risk patients are likely to achieve 90% response to single-agent chemotherapy, whereas high-risk patient will need multi-agent chemotherapy (Lurain et al. 1991).

After successful treatment for GTD, it is imperative to follow the patient with serial beta-hCG levels weekly until undetectable levels are noted for 3 weeks. Monthly beta-hCG measurements should then be drawn for 6–12 months. Six months follow-up may be sufficient if the decline in beta-hCG follows the normal regression curve as detailed by Morrow et al. (1977). However, 12 months follow-up is recommended if regression is irregular. During the monitoring for declining serial beta-hCG, it is necessary for the patient to be on effective contraception. A concomitant pregnancy at the time of beta-hCG evaluation will lead to an inability to monitor for disease recurrence. The intrauterine device, however, is not recommended as birth control for patients with GTD given the risk for uterine perforation. Oral contraceptive pills and implantable devices are both safe for use (Berkowitz and Goldstein 2009).

Table 3 FIGO staging system

Stage	Extent of disease
I	Limited to the uterus
II	Extension beyond uterus to adnexa, broad ligament, or the vagina
III	Extension to the lungs with or without extension to genital tract
IV	Other metastatic sites

Adopted and modified from FIGO Committee on Gynecologic Oncology (Oncology 2009)

2 Management of Primary GTN

Primary GTN is highly curable with chemotherapy. Primary treatment is dictated by the WHO and FIGO score as above. A WHO score of 6 or less with FIGO stages I–III is considered to be low-risk disease and can be treated with a single chemotherapeutic agent. A score of 7 or greater with FIGO stages I–III or FIGO stage IV is considered to be high-risk disease and calls for treatment with a combination of agents.

Table 4 WHO prognostic scoring system

Score assigned	0	1	2	4
Age at diagnosis	Less than 40	40 or greater	-	-
Prior pregnancy	Mole	Abortion	Term	-
Interval between index pregnancy (months)	Less than 4	4–6	7–12	More than 1 year
Pretreatment beta-hCG	Less than1000	1000–10,000	10,000–100,000	Greater than 100,000
Tumor size (cm); including uterine mass size	Less than 3	Greater than 3 but less than 5	5 or greater	-
Metastatic location	Lung*	Kidney/spleen	GI	Brain or liver
Number of metastases	0	1–4	5–8	9 or more
Failed chemotherapy	-	-	Single agent	Multi-agent

*Lung metastases should only be included in the WHO score if seen on Chest X-Ray (CXR). Lung CT-Scan may be used but should not influence the score because of the likely presence of lung micro-metastases. If counted, they would increase the score without adding any clinical benefit. While a lung metastasis receives a score of 0, it may be included when counting the total number of metastatic lesions if visualized on CXR

Adopted and modified from FIGO Committee on Gynecologic Oncology (Abrão et al. 2008; Oncology 2009)

Table 5 Response rate for chemotherapy regimens for low-risk GTN

Regimen	Primary Remission Rate (%)
(a) MTX 0.4 mg/kg IM for 5 days, repeated q2 weeks	87–93
(b) MTX 50 mg IM or 1 mg/kg QOD for four doses with leucovorin 15 mg or 0.1 mg/kg administered 24–30 h after each MTX dose	74–90
(c) MTX 30 mg/m^2 or 50 mg/m2 IM given weekly	49–74
(d) Act-D 1.25 mg/m^2 IV q2 weeks (pulsed regimen)	69–90
(e) Act-D 12 μg/kg for 5 days, repeated q2 weeks	77–94
(f) (i) MTX 20 mg IM on D1–D5 with 500ug Act-D IV on D1–D5 q2 weeks (ii) Act-D 0.6 mg/m^2 on D1 and D2 with MTX 100 mg/m^2 IV push and then infusion of 300 mg/m^2 on D1–D2 followed by leucovorin for 2 weeks	100

Adopted and modified from Lurain (2011)
Abbreviations: *MTX*, methotrexate; *Act-D*, actinomycin D; *QOD*, every other day; *q2 week*, every 2 weeks

2.1 Low-risk GTN: Chemotherapy

As mentioned above, low-risk GTN is usually treated with single-agent chemotherapy. Two agents are typically used for treatment of low-risk disease, methotrexate and actinomycin D with cure rates of approximately 100%. Etoposide was historically used for low-risk disease, but this has fallen out of favor due to the slightly increased risk of secondary malignant tumors, especially leukemia (Rustin et al. 1996). Several different dosing regimens have been studied for methotrexate and actinomycin D; these are discussed below. Table 5 summarizes the regimens and includes their primary remission rates.

(a) Methotrexate 0.4 mg/kg intramuscularly (IM) for 5 days, repeated every 2 weeks. The primary failure rate is approximately 11% for non-metastatic disease (Lurain and Elfstrand 1995). The response rate in women with metastatic disease has been quoted to be 60% (Soper et al. 1994).

(b) Methotrexate with folinic acid (leucovorin) rescue: Methotrexate 50 mg IM or 1 mg/kg every other day for four doses with leucovorin 15 mg or 0.1 mg/kg administered 24–30 h after each methotrexate dose. In patients with nonmetastatic disease, only 7.7% of those treated with methotrexate alone developed resistant disease requiring a change in chemotherapy for induction of remission, while 27.5% of patients initially treated with the leucovorin rescue required a change in regimen to achieve remission. Thus, the frequency of drug resistance is significantly higher in those treated with the leucovorin rescue (Matsui et al. 2005). However, the use of methotrexate alone has been shown to be more toxic than the methotrexate-folinic acid combination.

(c) Methotrexate 30 mg/m^2 or 50 mg/m^2 IM given weekly. This regimen was used in GOG-174 to compare response rates to those of actinomycin D 1.25 mg/m^2 IV every 2 weeks (Osborne et al. 2011). Actinomycin D was found to be more effective with a response rate of 70% compared to 53% for weekly methotrexate.

(d) Actinomycin D 1.25 mg/m^2 IV every 2 weeks (pulsed regimen). Actinomycin D is associated with alopecia and is therefore less favored by patients.

(e) Actinomycin D 12 μg/kg for 5 days. This is an alternative to the 5-day methotrexate regimen. This regimen has shown to be effective in patients who failed to respond to the 1.25 mg/m^2 pulse actinomycin D regimen with an 80% response rate (Kohorn 2002).

(f) Combined methotrexate and actinomycin D: The following dosing regimens have been used for this combination regimen:

(i) Methotrexate 20 mg IM on D1–D5 with 500 μg actinomycin D IV on D1–D5 every 14 days (Abrão et al. 2008).

(ii) Actinomycin D 0.6 mg/m^2 on D1 and D2 with methotrexate 100 mg/m^2 IV push and then infusion of 300 mg/m^2 on D1–D2 followed by leucovorin for 14 days (Eiriksson et al. 2012). Higher remission rates have been reported when the combination is used as compared to each drug alone. It is has also proven to lead to a cure faster, requiring a fewer number of cycles (Eiriksson et al. 2012). The combination regimens ultimately yielded a greater number of grades 3 and 4 toxicities as defined by the Common Terminology Criteria of Adverse Events (CTCAE). Therefore, taking into consideration the frequency of toxic effects and a modest increase in remission rate, a combined regimen may be better suited for second-line therapy (Abrão et al. 2008).

GOG-275 is an ongoing multicenter phase III randomized control trial that compares the use of multiday methotrexate versus actinomycin D in treating patients with low-risk GTN. At present, the question of whether methotrexate versus actinomycin D should be used as first-line treatment for GTN remains unanswered (Alazzam et al. 2012a). While GOG-174 attempted to answer this question, it used the weekly methotrexate regimen which has been shown to be inferior to the multiday regimen. A Cochrane review meta-analysis concluded that actinomycin D is much more likely to achieve a primary cure when compared to methotrexate (82% in the actinomycin D group compared to 53% in the methotrexate group); however, the review included data from different dosing regimens making it difficult to draw a clear conclusion. The results from GOG-275 will help determine whether actinomycin D or methotrexate should be first-line choice for treatment of low-risk GTN (Alazzam et al. 2012a).

In general, treatment should be continued beyond the first negative beta-hCG titer; this is known as consolidation therapy (Lybol et al. 2012). Usually 2–3 cycles of chemotherapy are recommended, especially if the decrease in beta-hCG is slow or if there is extensive disease.

2.2 Low-risk GTN: Adjuvant Surgery

2.2.1 Second Curettage

Attempts have been made to curtail chemotherapy in the setting of low-risk GTN. The theory behind a second curettage is that debulking the tumor will lead to a decreased need for chemotherapy. Single institution retrospective studies have reported varying outcomes. The Dutch published a retrospective cohort study evaluating the effect of a second curettage on low-risk GTN (van Trommel et al. 2005). Their primary outcome measures were the need for chemotherapy and the number of chemotherapy courses required. Unfortunately, only 9.4% of patients were cured after curettage and required no further chemotherapy. However, those patients who received a second curettage required a fewer number of chemotherapy cycles, and the authors concluded that the second curettage offers a "debulking" effect. A second curettage is not without complications; 4.8% of patients in this study had a major complication such as uterine perforation and hemorrhage. Another retrospective study from the United Kingdom concluded that 60% of their patients did not require chemotherapy after a second evacuation (Pezeshki et al. 2004).

Until recently there was only one published prospective study from Iran evaluating the clinical response to a second curettage, with a small sample size of 12 (Yarandi et al. 2014): 83% of patients did not require chemotherapy and were cured by a second curettage. Eight percent of patients experienced a complication such as uterine perforation.

A second curettage has not been considered standard practice. Most practitioners believe that a second curettage should be reserved for patients who experience significant vaginal bleeding and anemia after the first curettage. The GOG recently published a multicenter prospective phase II study evaluating the efficacy and safety of a second curettage in lieu of chemotherapy for patients with low-risk GTN (persistent GTD). The study population included women with non-metastatic low-risk GTN. Patients whose first curettage revealed choriocarcinoma, PSTT, or ETT were

Table 6 Efficacy of second curettage for persistent GTD/low-risk GTN

Author	Year	Study type	No.[a]	Response rate (%)	Complication rate
van Trommel et al. 2005	2005	Retrospective, multicenter	85	9.4	4.8 %
Pezeshki et al. 2004	2004	Retrospective, multicenter	282	60	n.a.
Yarandi et al. 2014	2014	Prospective, single institution	12	83	8 %
Osborne et al. 2016	2016	Prospective, multicenter	60	40	10 %

[a]Patients who underwent second curettage for persistent GTD

excluded. Patients with previously treated low-risk GTN were excluded. The method of evacuation was not specified by the study but could include intraoperative ultrasound localization of the residual trophoblast or directed hysteroscopic resection. Forty percent of the patients were cured after the second curettage with only 10% of patients experiencing a complication. 1.6% of patients experienced uterine perforation that was managed by observation, 6.7% grade 1, and 1.6% grade 3 incidents of uterine hemorrhage as defined by the CTCAE 3.0. They concluded that a second curettage as initial treatment for low-risk GTN cures 40% of patients without significant morbidity (Osborne et al. 2016).

Table 6 provides a summary of the above-referenced studies evaluating the use of second curettage in the setting of low-risk GTN. Generally, the decision for second curettage should not be taken lightly, and patients must be counseled regarding the risks including hysterectomy if profuse bleeding and/or uterine perforation are encountered. Whether or not to perform a second curettage should be determined on a case-by-case basis given that methotrexate and actinomycin D are generally well tolerated and have excellent response rates.

2.2.2 Adjuvant Hysterectomy

Historically, the accepted indications for hysterectomy in women with GTN were removal of chemoresistant disease and to control hemorrhage or infection in emergency cases. However, a hysterectomy can be employed to help decrease the amount of chemotherapy required for treatment of low-risk GTN. The Japanese published a prospective trial evaluating the efficacy of adjuvant hysterectomy in women with and without metastatic disease (Suzuka et al. 2001). They treated 115 women with single-agent chemotherapy (the majority treated with etoposide) and then performed interval hysterectomy. Adjuvant hysterectomy decreased the total dose of etoposide given to achieve primary remission in women with nonmetastatic disease. There was no difference in the number of chemotherapy cycles required for remission in patients with metastatic disease. Thus, the authors concluded that adjuvant hysterectomy is a viable option for women who have completed childbearing and whose disease is confined to the uterus. Another study also concluded that adjuvant hysterectomy significantly reduced the amount of chemotherapy used to achieve remission (Hammond et al. 1980).

2.3 High-Risk GTN: Chemotherapy

Unlike treatment of low-risk GTN, high-risk GTN should be treated with combination regimens, as opposed to single-agent therapy. High-risk GTN patients are at risk of developing drug resistance to methotrexate when it is used as a single agent. Below are the most widely studied combination regimens and associated toxicities:

(a) Cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan, and vincristine (CHAMOMA). In 1981 the GOG instituted a prospective randomized protocol comparing CHAMOMA and methotrexate, actinomycin D, and chlorambucil (MAC) (Curry et al. 1989). At that time, MAC was the standard of care for patients with high-risk disease, and their goal was to find a less toxic

Table 7 EMA-CO regimen

Day	Agents	Dosing
1	Etoposide	100 mg/m^2 IV over 30 min
	Actinomycin D	0.5 mg IV push
	Methotrexate	100 mg/m^2 IV and 200 mg/m^2 IV in 1000 mL of D5W over 12 h
2	Etoposide	100 mg/m^2 IV over 30 min
	Actinomycin D	0.5 mg IV bolus
	Folinic acid	15 mg IM or PO every 12 h for four doses starting 24 h after initiation of methotrexate
8	Cyclophosphamide	600 mg/m^2 IV
	Vincristine	1.0 mg/m^2 IV push

Adopted and modified from Escobar et al. (2003)
Repeat cycle on days 15, 16, and 22 (every 2 weeks)

and more effective regimen. The study, however, concluded the opposite; the CHAMOMA regimen was more toxic and possibly less effect. It closed prematurely because of a 30% death rate in the CHAMOMA arm, compared to a 4% death rate in the MAC arm.

(b) MAC: This regimen has a response rate of approximately 77% and was routinely used up until the 1990s when the combination regimen of EMA-CO was found to be well tolerated and has a response rate of approximately 83% (Curry et al. 1989) (Bower et al. 1997). EMA-CO has now become the preferred first-line combination regimen in the United States and Europe.

(c) MEA: This regimen, like EMA-CO, uses etoposide, methotrexate, and actinomycin D but omits the use of etoposide and Oncovin (vincristine); it has a 74.4% response rate (Matsui et al. 2000). It has been favored by some European centers because of its tolerability.

(d) 5-Flurouracil, methotrexate, etoposide (5-FUME): This regimen is mostly used in China and has an 80.8% remission rate in high-risk patients, which appears to be comparable to the published results seen with EMA-CO. It also appears that the toxicity profile of this regimen may be slightly better than that of EMA-CO. However, this regimen is far less studied, and further investigation is warranted (Wang et al. 2006).

(e) EMA-CO: In the late 1970s, it was discovered that etoposide was a very effective chemotherapeutic agent for GTD. EMA-CO was subsequently formulated by Newlands et al. (1986). Table 7 outlines the treatment regimen. As mentioned above, complete response rates and long-term survival rates of well over 80% have been reported with this regimen (Newlands et al. 1991). The toxicities of this regimen are manageable with the most common being anemia and neutropenia which may require a treatment delay of about a week (Schink et al. 1992; Escobar et al. 2003). Colony-stimulating factors (G-CSF 300 μg subcutaneous) can be administered on days 9–14 of the cycle if any neutropenia-related treatment delays are experienced. Treatment delays should be minimized as resistance can develop if interruption is experienced. This regimen is now the preferred first-line regimen for high-risk GTN.

3 Management of Refractory/Persistent Disease

GTN that does not respond to first-line treatment is said to be resistant or refractory. Resistance to a particular chemotherapeutic regimen is evidenced by a plateau or rise in beta-hCG levels. Approximately 5% of low-risk patients and 25% of high-risk patients will have an incomplete response or experience a recurrence following the first-line therapy (Lurain and Nejad 2005). In this setting, salvage chemotherapy and surgical resection, when appropriate, are employed. A new WHO score must be assigned, and treatment is once again determined based on low- versus high-risk WHO score.

Table 8 EMA-EP schedule

Day	Agents	Dosing
EP		
1	Etoposide	150 mg/m^2 IV in 250 mL NS over 30 min
	Cisplatin	25 mg/m^2 IV in 1 L NS + 20 mmol KCL 4 h
EMA		
1	Etoposide	100 mg/m^2 IV in 250 mL NS over 30 min
	Methotrexate	300 mg/m^2 IV in 1 L NS over 12 h
	Actinomycin D	0.5 mg IV bolus
2	Folinic acid	15 mg PO or IM[a] BID for four doses 24 h after start of methotrexate

Adopted and modified from Newlands et al. (2000)
EP and EMA are alternated at weekly intervals
[a]The decision as to route of administration depends on development of nausea and ability to tolerate oral intake

3.1 Low-Risk Refractory GTN

In treating low-risk GTN, if resistance to methotrexate is noted, it is common practice to use the sequential 5-day actinomycin D, followed by MAC or EMA-CO if further salvage treatment is required (Alazzam et al. 2012b).

3.2 High-Risk Refractory/ Recurrent GTN

Patients with persistent or recurrent high-risk GTN who develop resistance to methotrexate-containing regimens should be treated with platinum-containing combination regimens.

EMA-EP substitutes etoposide and cisplatin for cyclophosphamide and Oncovin in the EMA-CO protocol and is commonly the initial approach employed for patients who responded to EMA-CO and have plateauing beta-hCG levels or experience a recurrence (Table 8) (Lurain and Nejad 2005). Response rates can be as high as 75% in patients who previously failed EMA-CO. This regimen is moderately toxic; in particular it can be nephrotoxic and myelosuppressive, thus renal function must be closely monitored (Newlands et al. 2000).

Other regimens have also been described for use in this setting: BEP (bleomycin, etoposide, and cisplatin), VIP (vinblastine, ifosfamide, and cisplatin), ICE (ifosfamide, cisplatin, and etoposide), and TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide) (Lurain and Nejad 2005); (Wang et al. 2008). At the Brewer Trophoblastic Disease Center, BEP is the first choice for treating high-risk patients who are resistant to EMA-CO/EMA-EP (Lurain and Nejad 2005). Charing Cross Hospital in London has presented TP/TE as an effective, relatively well-tolerated salvage regimen for patients with heavily pretreated high-risk GTN (Wang et al. 2008).

Figure 1 provides a proposed chemotherapy treatment algorithm for both low-risk/high-risk GTN and refractory disease as described above. It is important to note that refractory cases should be referred to a trophoblastic disease center for consultation.

3.3 Non-gestational Trophoblastic Tumors (Non-GTT)

In the setting of high-risk refractory GTN, one must also think of and evaluate for non-gestational trophoblastic tumors (Alifrangis et al. 2013). These are choriocarcinomas that are not associated with pregnancy. Oftentimes, the distinction can be made on histopathology by finding the absence of syncytiotrophoblasts. However, some non-GTTs can exhibit trophoblastic differentiation making the distinction difficult. Genetic testing of the tumor with microsatellite genotyping can be employed to examine the genetic origin of these tumors (Fisher et al. 2007). Non-GTTs do not respond to chemotherapy and have a very poor prognosis; being able to distinguish between GTT and non-GTT helps optimize patient care.

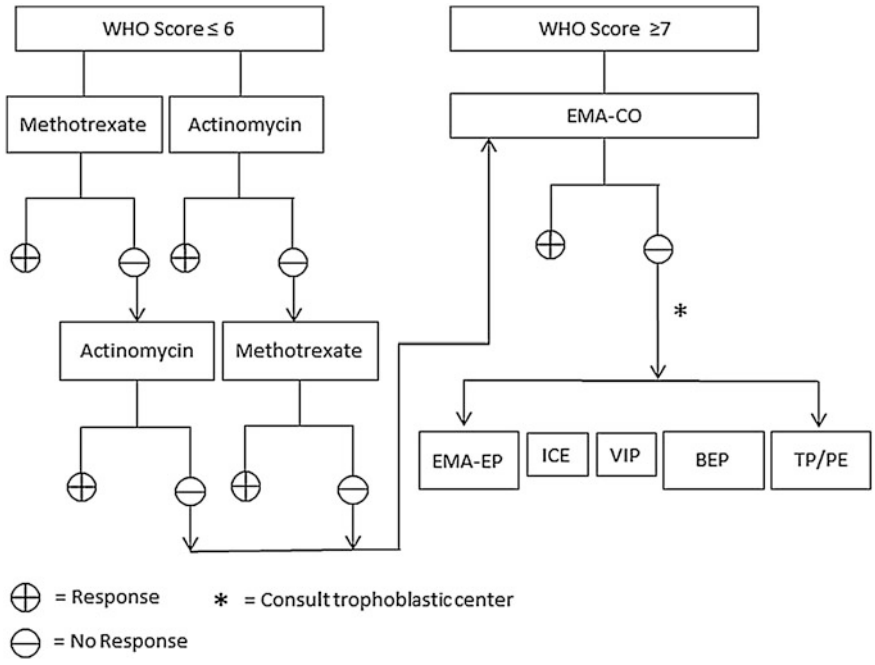

Fig. 1 Proposed chemotherapy treatment algorithm. Abbreviations: *WHO*, World Health Organization; *EMA-CO*, etoposide, methotrexate, actinomycin D, cyclophosphamide, and Oncovin; *EMA-EP*, etoposide, methotrexate, actinomycin D, etoposide, and cisplatin; *BEP*, bleomycin, etoposide, and cisplatin; *ICE*, ifosfamide, cisplatin, and etoposide; and *TP/TE*, paclitaxel, cisplatin/paclitaxel, etoposide

4 Special Considerations

4.1 Vaginal Metastases

The incidence of vaginal metastasis in choriocarcinoma is 8.6% (Yingna et al. 2002). The vagina is the second most common metastatic site in GTN, with the lung being the most common. These patients present with friable, vascular lesions located in the anterior wall of the lower vagina. Though performing a biopsy for diagnostic conformation may be tempting, it puts the patient at great risk for hemorrhage and is therefore discouraged when metastatic GTN is suspected. If patients present with spontaneous hemorrhage, vaginal packing with the use of hemostatic agents should be employed. Selective angiographic embolization by interventional radiology is another viable option in the setting of acute hemorrhage. Treatment for vaginal metastasis includes systemic treatment with chemotherapy as well as local injection with 5-FU (Yingna et al. 2002).

4.2 Brain Metastases

Metastases to the brain and central nervous system (CNS) are observed in up to 10–15% of patients with GTN. CNS involvement is frequent enough that it is one of the criteria used to assign patients to the high-risk category. Treatment of CNS metastasis has evolved to include whole brain radiation (WBRT). It has shown to have significant therapeutic benefit in the treatment of GTN with improved overall survival. The survival of patients with metastatic GTN to the brain is excellent if extracranial disease is controlled (Schechter et al. 1998). It is recommended that WBRT be initiated simultaneously with the start of multi-agent systemic chemotherapy (Yordan et al. 1987). Should chemotherapy be initiated before WBXRT there is increased risk of intracranial hemorrhage.

Treatment initiation with WBRT can reduce the incidence of hemorrhage and resultant sequela in the first 2 weeks of chemotherapy administration (Schechter et al. 1998).

When treating patients with brain metastases, the systemic dose of methotrexate administered IV must be increased because the concentrations of methotrexate in the cerebrospinal fluid have been found to be less than 5% of plasma concentrations. The use of high-dose methotrexate regimens without concomitant WBRT has achieved remission rates as high as 69%; the addition of WBRT can increase remission rates to 78% (Schechter et al. 1998).

Intrathecal chemotherapy in conjunction with systemic chemotherapy has also been evaluated in the setting of CNS metastasis and has yielded excellent survival rates (Small et al. 1996). A direct comparison between intrathecal chemo administration and WBRT has yet to be made. However, it appears that treatment with WBRT is more commonly employed.

WBRT is not without toxicity. It can lead to long-term sequelae including impaired cognitive function, dementia, behavioral changes, and ataxia. For this reason, in the setting of a solitary brain lesion, craniotomy with surgical resection should be employed in efforts to avoid WBRT. More recently, the use of stereotactic radiosurgery has been employed and reported by Charing Cross to treat multiple brain metastases or solitary lesions in locations that are inaccessible with surgery (Soper et al. 2007).

If a CNS recurrence is suspected during surveillance and no lesion is noted on imaging, a plasma to spinal fluid ratio can be obtained. In the absence of brain metastases, the spinal fluid beta-hCG level is proportional to that of plasma. A plasma to spinal fluid ratio less than 60 is confirmatory of CNS recurrence (Bagshawe and Harland 1976). Overall patients with brain metastases have a good prognosis; however, those who develop brain metastases during treatment with systemic therapy or recur to brain after WBRT have the poorest prognosis (Evans et al. 1995).

4.3 Reproductive Outcomes After Treatment for GTN

GTN affects women of reproductive age; thus, fertility and reproductive outcomes following treatment are of utmost importance. Studies evaluating the reproductive outcome of patients treated for both low- and high-risk GTN have concluded that reproductive outcomes do not differ from the general population. In addition the chemotherapy regimen does not affect reproductive performance when comparing single-agent methotrexate to multi-agent therapy (Woolas et al. 1998). However, data regarding the risk of congenital malformation appears to be conflicting; while some studies conclude that the risk is similar to that of the general population in both frequency and type for both single and multi-agent therapy, another concluded that the risk of congenital heart abnormalities (particularly ventricular septal defects) is higher in the group receiving multi-agent treatment (Goto et al. 2004). The overall risk of congenital anomalies is relatively low but should be discussed with patients receiving multi-agent therapy for GTN. The American Society of Clinical Oncology stresses the importance of discussing the potential for infertility with all patients undergoing treatment for cancer. While treatment for GTN appears to have minimal effect on reproductive outcomes, the possibility of infertility should be addressed and documented.

4.4 Post-molar Prophylactic Chemotherapy

To date, the use of chemotherapy for primary prevention of post-molar GTN remains controversial as there is conflicting data regarding efficacy (Ayhan et al. 1990). Patients with high-risk hydatidiform moles, as defined in Table 9, have up to a 50% chance of developing post-molar GTN (Uberti et al. 2009). It has been argued that chemotherapy administered at the time of uterine evacuation in this patient population can prevent the development of GTN; however, studies have shown that prophylactic

Table 9 Risk scoring system for the prediction of developing GTN in women with a molar pregnancy

Score	0	1	2	3
Ultrasound diagnosis of HM in current pregnancy	Partial	Complete	Recurrent	-
Uterine size for gestational age at diagnosis of molar pregnancy	Size = or < dates	Size 4 weeks greater than corresponding gestational age	Size 8 weeks greater than corresponding gestational age	Size 12 weeks greater than corresponding gestational age
Beta-hCG levels (mU/mL)	<50,000	50,000–100,000	100,000–1,000,000	>1,000,000
Diameter of theca lutein cyst (cm)	-	<6	6–10	>10
Patient's age (years)	-	<20	≥40	>
Associated medical complications[a]	-	≥1	-	-

Adopted and modified from Uberti et al. (2006)
Final score of <4 is low risk; ≥4 is high risk
HM, hydatidiform mole
[a]Hyperthyroidism, hyperemesis, preeclampsia, trophoblastic embolization, disseminated intravascular coagulation

chemotherapy is not without risk. Those who receive chemoprophylaxis are known to have prolonged hospital stays and chemotherapy-related toxicities and require more courses of chemotherapy to cure subsequent GTN, all of which may seem too risky for a disease with an excellent cure rate. Nevertheless, it does not affect reproductive outcomes and has also been shown to reduce psychological angst, medical visits, and operational costs associated with management of post-molar GTN/persistent GTD (Uberti et al. 2009). Though the use of chemoprophylaxis is not widely accepted, most agree that its use is most appropriate for patients with high-risk moles in settings where serial beta-hCG levels cannot be followed and in those with poor compliance, such as in the adolescent population (Uberti et al. 2006). Table 9 offers a scoring system for the prediction of developing GTN in women with a molar pregnancy. Women with a score of greater than or equal to 4 are deemed to be high-risk of developing GTN and may benefit from post-molar prophylactic chemotherapy. Table 10 provides a summary of the published studies evaluating the efficacy of post-molar chemoprophylaxis. Methotrexate administered at 0.4 mg/kg IM for 5 days did not prove effective for post-molar prophylaxis. However, actinomycin D at 1.25 mg/m^2 IV X 1 dose has shown to reduce the rate of post-molar GTN in high-risk molar pregnancies.

Table 10 Summary of prophylactic chemotherapeutic regimens and response

Chemotherapy	Schedule	Rate of post-molar GTN in high-risk mole Control versus Prophylactic Chemotherapy
Methotrexate (Ayhan et al. 1990)	0.4 mg/kg IM, 5 days	26.2% vs 25%
Actinomycin D (Uberti et al. 2009)	1.25 mg/m^2 IV, one dose	34.3% vs 18.4%
Actinomycin D (Uberti et al. 2006)	1.25 mg/m^2 IV, one dose	29% vs 6.9%

4.5 Phantom Beta-hCG, Quiescent GTD, and Physiologic Beta-hCG

After treatment for GTN is complete, it is recommended that quantitative serum beta-hCG levels be followed monthly for 6–12 months after normalization as the risk of relapse is about 3% during the first year and significantly decreases

thereafter (Lurain 2011). Women with persistent mildly elevated beta-hCG levels can exhibit false-positive results caused by non-specific heterophilic antibodies. This can lead to unnecessary workup and treatment intervention for presumed persistent or recurrent disease. Two criteria have been developed to identify false-positive beta-hCG levels: (1) elevated serum beta-hCG levels in the setting of a negative urine pregnancy test and (2) finding of more than a fourfold difference between commercially available immunoassays employed in the common clinical setting and those used by reference laboratories (Rotmensch and Cole 2000).

False-positive beta-hCG must be differentiated from quiescent GTD. Quiescent GTD is defined by persistent low levels of beta-hCG present for at least 3 months with no changed in beta-hCG trend. It is caused by a small focus of persistent slow-growing syncytiotrophoblasts that produce low levels of beta-hCG but do not typically progress to invasive disease (Cole 2010). Testing for hyperglycosylated hCG (h-hCG) can be employed to discriminate quiescent GTD from active trophoblastic malignancy. Quiescent GTD does not respond to chemotherapy. H-hCG is produced by invasive cytotrophoblasts and therefore a marker of invasive cells. It can be used by clinicians to decide when treatment is not indicated but also help detect active disease at its inception so that appropriate treatment can be initiated (Cole et al. 2006).

Low levels of physiologic beta-hCG are secreted from the pituitary alongside luteinizing hormone (LH) during the LH surge of the ovulatory cycle. Pituitary beta-hCG production increases with age and is frequently detected in perimenopausal or postmenopausal women. Physiologic expression of beta-hCG has led to unnecessary treatment for GTN. Pituitary expression of beta-hCG can be suppressed with a short course of combined oral contraceptives and can help rule out GTN (Cole et al. 2008).

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Survivorship of Gynecologic Malignancy

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Abstract

As screening and cancer treatment has improved, the number of women who are survivors of gynecologic malignancies is increasing. Gynecologic cancer survivors may present a unique challenge for gynecologists and practitioners who find themselves caring for these women. Understanding their unique psychosocial, sexual, and residual treatment symptoms as well as understanding surveillance and screening guidelines will help improve the care of this population.

Keywords

Survivorship • Cancer survivor • Gynecologic cancer • Women's cancer • Cancer follow-up

1 Introduction

Advances in cancer diagnosis and treatment have led to a steady increase in the number of cancer survivors, a population with unique physical, psychosocial, and economic needs. In recent decades, coordinated efforts have focused on understanding this population and on enhancing the length and quality of life of survivors. In 1996, the National Cancer Institute created the Office of Cancer Survivorship, and in recent decades increasing research has investigated diverse aspects of survivorship (American Cancer Society 2014; National Institute of Cancer, Office of

Cancer Survivorship; National Research Council 2005).

An individual is considered a survivor from the time of cancer diagnosis for the remainder of his or her life. The survivorship experience can be divided into phases including an acute treatment phase, an intermediate survivor phase, and a long-term survivor phase. Caregivers are also included as survivors, as their lives may be affected significantly by others' cancer diagnoses. General survivorship care encompasses surveillance of the primary malignancy, managing complications of the cancer or its treatment, risk reduction and screening for second malignancies, and assessment of overall quality of life and psychosocial well-being (American Cancer Society 2014; National Research Council 2005).

The number of gynecologic cancer survivors has grown substantially in recent decades, most notably among those diagnosed with early stage disease. In the United States, there are currently an estimated 625,000 survivors of endometrial cancer, 244,000 survivors of cervical cancer, and nearly 200,000 survivors of ovarian cancer, in total accounting for about 15 % of all female cancer survivors (American Cancer Society 2014). As the number of cancer survivors increases, the general gynecologist can expect to care for women with a history of female genital cancers.

2 Effects of Gynecological Cancer and Treatment

2.1 Psychosocial Issues

Attempting to understand and address the psychosocial challenges faced by cancer survivors is an established and important aspect of survivorship care and research (National Research Council 2005). Proceeding with life after cancer can be a complicated, life-altering process. The psychological evolution that occurs during this process can result potentially in both positive and negative outcomes among survivors (Thornton and Perez 2006).

Struggles commonly described by cancer survivors include fear, uncertainty, anxiety, depression, insomnia, relationship challenges, employment discrimination, financial concerns, and loss of insurance (Wenzel et al. 2002; Roland et al. 2013; Meyer and Mark 1995; Hodgkinson et al. 2007; Kirchhoff et al. 2012; Bodurka et al. 2005). Furthermore, due to disease and treatment specifics, gynecologic cancer survivors may frequently encounter issues with body image, sexuality, and fertility (Carter et al. 2005; Bukovic et al. 2008). Compared to other populations of cancer survivors, relatively few studies have specifically investigated the long-term psychosocial outcomes and needs of gynecologic cancer survivors. Caution must be emphasized when generalizing among survivors as each population faces unique challenges and has specific supportive care needs.

It has been recognized that medical variables, while important, seem to play a lesser role than psychological adjustment in predicting long-term psychological health among survivors (Hodgkinson et al. 2007; Carver et al. 2006). Studies have suggested that survivors with better social support systems experience less anxiety and depression (Kimmel et al. 2014; Carpenter et al. 2010) and that socioeconomic status may strongly contribute to overall wellbeing (Greenwald et al. 2014). A recent longitudinal study investigating long-term survivors of gynecologic cancers revealed overall normal levels of quality of life and relationship adjustment, however, increased levels of anxiety, and posttraumatic stress disorder among survivors (Hodgkinson et al. 2007). Overall, more research is needed in this area.

In general, cancer survivors as a whole have fortunately shown positive responses to psychosocial interventions (Meyer and Mark 1995). Unfortunately, many survivors do not receive psychosocial care (Forsythe et al. 2013), representing missed opportunities. Thus, we recommend routine psychological screening and emphasize that screening should continue throughout a survivor's life, as a longer survivorship period does not necessarily correlate with decreased psychosocial concerns (Hodgkinson et al. 2007). There are

multiple brief psychosocial distress scales available for rapid in-office screening (National Cancer Institute). When psychological issues are identified, we recommend either treating or promptly referring for treatment.

Other interventions that have been associated with psychosocial well-being include healthy lifestyle interventions and management of menopausal symptoms. We recommend encouraging healthy lifestyle choices including healthy eating, regular exercise, and good sleep. Regular physical activity may positively affect survivors' psychosocial wellbeing and quality of life (Stevinson et al. 2007; Crawford et al. 2015). Menopausal symptoms, especially in premenopausal patients, have been associated with distress, depression, and sexual dysfunction (Carter et al. 2010). While most gynecologic cancer survivors can be treated with hormone replacement therapy (Biliatis et al. 2012), consult with the patient's oncologist if there is concern about tumor hormonal response. The American College of Obstetricians and Gynecologists also recommends several nonhormonal options for management of menopausal symptoms that may be of benefit to these women (American College of Obstetricians and Gynecologists 2014).

In addition, it is important to address survivors' supportive care needs, as increased unmet needs correlate with increased distress and decreased quality of life (Hodgkinson et al. 2007). Referral to a well-run local survivor support group may be helpful and can often be located through local chapters of the American Cancer Society (Sanson-Fisher et al.). Relationship counseling may be beneficial, especially among younger survivors (Kirchhoff et al. 2012). Finally, sexual dysfunction and infertility, to be discussed subsequently, may profoundly affect survivors' psychological health and social wellbeing (Carter et al. 2005, 2010).

2.2 Sexual Health

Among cancer survivors in general, sexual dysfunction has been broadly identified as a common and often untreated problem (Sadovsky et al. 2010). Women treated for gynecologic malignancies are at risk for sexual dysfunction due to the nature, location, and treatment of their disease. After all, patients with gynecological cancer often undergo pelvic surgery and/or pelvic radiation, which may have considerable effects on sexual function (Donovan et al. 2007). Research has indicated that sexual concerns among gynecologic cancer survivors may include physical, psychological, and social dysfunctions (Abbott-Anderson and Kwekkeboom 2012). A recent abstract presented at the 2015 American Society of Clinical Oncologists found that young, premenopausal women, those who underwent chemotherapy and those in committed relationships, may be at greater risk for sexual dysfunction, and among those with sexual dysfunction, a greater decline in sexual activity was seen after cancer treatment (Guntupalli et al. 2015).

Pelvic radiation therapy may contribute significantly to many of the physical effects described, including skin fibrosis, shortening and narrowing of the vagina, disruption in ovarian function and subsequent vaginal dryness, dyspareunia, and loss of interest in sexual activity (Donovan et al. 2007; Aerts et al. 2009; Bergmark et al. 1999; Amsterdam and Krychman 2006). Other concerns identified among gynecologic cancer survivors include altered body image, decreased libido, sexual performance anxiety, and perceived changes in partner interest (Bourgeois-Law and Lotocki 1999; Bukovic et al. 2008; Carmack Taylor et al. 2004; Corney et al. 1993; Juraskova et al. 2003; Lindaw et al. 2007).

When considering treatment options for cancer-related sexual dysfunction, it is important to recognize that normal sexual functioning can vary markedly and that sexual function may improve as time from treatment increases (Sadovsky et al. 2010; Vaz 2011). Therapies addressing sexual dysfunction may focus on physical or psychosocial components. Studies evaluating various interventions are few and have shown mixed results (Abbott-Anderson and Kwekkeboom 2012; Brotto et al. 2008; Robinson et al. 1994; Miles and Johnson 2014).

We recommend screening all gynecologic cancer survivors for sexual dysfunction and offering therapeutic suggestions to interested patients.

Optimal evaluation and treatment often requires a multidisciplinary team. Physical concerns are often related to loss of ovarian function and anatomical changes resulting from treatment. Although conclusive evidence does not exist regarding the efficacy of vaginal dilator use (Miles and Johnson 2014), use of a graduated series of dilators with lubricant may improve vaginal compliance, dyspareunia, and sexual function. Vaginal dryness may be improved with use of a vaginal moisturizer or a local estrogen product (Carter et al. 2001). We also recommend screening for underlying psychological disorders. In addition, relationship counseling or consultation with a sexual therapist may benefit some patients.

2.3 Fertility Implications

While the majority of women diagnosed with gynecologic cancer are postmenopausal, a significant number are of reproductive age. Clinicians must be aware of the reproductive consequences of treatments, which can profoundly affect a woman's reproductive potential and overall wellbeing. Studies have shown that women with absent or impaired fertility resulting from gynecologic cancer treatment may experience depression, grief, and stress resulting from infertility (Carter et al. 2005; Stevinson et al. 2007).

Gynecologic cancers are treated with some combination of surgery, radiation, and chemotherapy, any of which may negatively affect fertility. While surgery may remove part or all of a woman's reproductive organs, radiation and chemotherapy can significantly hinder ovarian function and subsequent ability to conceive. Pelvic irradiation and alkylating chemotherapeutic agents pose the greatest threats to ovarian function, but other chemotherapeutics may contribute. In addition, pelvic irradiation affects the uterus and may hinder pregnancy implantation and appropriate growth (Stroud et al. 2009).

As fertility has emerged as such a significant quality of life issue among cancer survivors, fertility preservation in patients undergoing gynecologic cancer treatment is an emerging topic. Reproductive aged women with fertility desires and early stage endometrial, cervical, and ovarian cancers are increasingly being offered fertility-conserving treatment options (Ditto et al. 2014, 2015; Koskas et al. 2014). The complicated medical, ethical, and legal details of such are beyond the scope of this article; however, this trend will undoubtedly affect future gynecologic cancer survivors. Gynecologic cancer survivors with fertility concerns should be promptly evaluated by a reproductive specialist in conjunction with their oncologists.

2.4 Loss of Ovarian Function and Bone Health

As discussed previously, premenopausal women may lose ovarian function as a result of gynecologic cancer treatment. While this may be quite disruptive to a woman psychologically, sexually, and socially (Carter et al. 2010), early loss of ovarian function may also have significant long-term effects on bone health (Stavraka et al. 2013). While further study in this area is needed, it is important to regularly screen affected women and encourage healthy eating, calcium supplementation, and regular weight-bearing exercise. ACOG has published recommendations for management of osteoporosis (American College of Obstetricians and Gynecologists 2012).

Providers may be concerned with offering survivors of gynecologic malignancies hormone replacement therapy, especially survivors of ovarian and endometrial cancers. For women with a personal history of ovarian cancer, a recent meta-analysis showed no increased risk of recurrence of disease in users HRT (Li et al. 2015). As the data supports a negligible or no increased risk for women developing ovarian cancer on hormones and there is no added risk of recurrence in patients with a personal history of ovarian cancer, HRT should be considered safe for the management of menopause symptoms in these women.

Exogenous estrogen use is associated with an increased incidence of endometrial cancer while progesterone is protective against type I uterine malignancies. Multiple studies have demonstrated

a regression of endometrial hyperplasia and low-grade endometrial cancers using various types of progestins (Santen et al. 2010). When estrogen is used in combination with progestin, there is no increased risk of uterine cancer over the general population. The Women's Health Initiative (WHI) investigated rates of endometrial cancer in postmenopausal women taking HRT to those taking a placebo. They found a small, non-significant decrease in the incidence of uterine malignancy, 56 versus 69 per 100,000 person-years compared to non-HRT users (Anderson et al. 2003). For women with a personal history of endometrial cancer, several trials have demonstrated no increased risk of recurrence of disease (Santen et al. 2010).

2.5 Lymphedema

Lower-extremity lymphedema is a late effect experienced by some gynecologic cancer survivors, especially those treated with surgery or radiation involving the pelvic or inguinal lymph nodes (Beesley et al. 2007). Onset may occur immediately after therapy or be delayed many years (Hareyama et al. 2015). Patients with lymphedema may complain of pain, heaviness, fullness, a tight sensation, or decreased flexibility in an affected limb. Simple activities of daily living may be affected, and ambulation may be difficult (International Society of Lymphology 2013). Physical exam findings may include nonpitting edema, and magnetic resonance imaging techniques are increasingly being used to diagnose early lymphedema (Brennan and Miller 1998).

Risk factors for developing lower extremity lymphedema include the extent of surgery or radiation to lymph nodes, removal of the circumflex iliac lymph nodes, cellulitis, and delayed wound healing (Brennan and Miller 1998; Abu-Rustum and Barakat 2007). Lymphedema may be instigated by small traumas including cuts, bites, injections, and sunburns. It is important for patients with lymphedema to maintain good skin hygiene and to engage in simple, regular range of motion exercises (International Society of Lymphology 2013). Therapies which may help survivors suffering from lymphedema include: lymphedema hosiery, manual massage, compression bandages, or consultation with a lymphedema therapist. Severe cases may require hospitalization and intravenous antibiotics (Beesley et al. 2007; International Society of Lymphology 2013; Brennan and Miller 1998). Lymphedema therapists may be located through the Lymphology Association of North America.

2.6 Cognitive Dysfunction

Cancer patients may suffer from cognitive dysfunction, which may persist long after completion of treatment. The individual patient, type of cancer, and variety of treatment all combine to influence a survivor's cognitive state. Factors that may contribute to cognitive dysfunction include: indirect effects of the cancer itself, brain metastases, chemotherapy, radiation therapy, medication effects, preexisting conditions, and psychiatric issues (Andreotti et al. 2015). Research exploring cognitive-related cancer dysfunction in survivors of gynecologic cancers is scant, as most literature in this area has focused on general or breast cancer survivors. However, cognitive decline has been identified among gynecologic cancer survivors and must be considered in survivor care plans (Correa et al. 2010; Sleight 2015; Donovan et al. 2007).

Interestingly, the cognitive deficits commonly described by survivors tend to differ from those of neurodegenerative diseases. Cancer patients and survivors often describe problems with organization, attention, memory, multitasking, and efficiency, often causing problems with occupational or social responsibilities (Falleti et al. 2005; Boykoff et al. 2009). Standard tests such as the Mini Mental Status Exam are often not sensitive enough to detect the subtle cognitive deficits experienced by survivors, and perceived cognitive decline may be considered reason to explore potential intervention (Sleight 2015).

When assessing cancer survivors with perceived cognitive dysfunction, it is important to address and treat fatigue, assess psychological

health, assess for anemia, and encourage healthy lifestyle habits. Potential interventions include cognitive behavior therapy, coping strategies such as assisted technology or memory aids, compensatory strategy training, stress management, and energy management (Sleight 2015; Ferguson et al. 2012; Goedendorp et al. 2014). It is also important to remember that a new cognitive deficit in a cancer survivor could be an indication of recurrence and requires prompt evaluation.

3 Long-Term Chemotherapy and Radiation Therapy Effects

Many different side effects of treatment can continue long after therapy is finished, sometimes lifelong. Some long-term side effects of radiation include vaginal narrowing and shortening, creating sexual dysfunction, radiation proctitis or cystitis, or skin break down. Long-term side effects of chemotherapy can include neuropathies, fertility issues, skin changes, and potential end-organ dysfunction. While many side effects can be treated symptomatically, specialty consultation should be sought for severe sequella.

4 Survivorship Issues by Gynecologic Cancer Type

4.1 Endometrial/Uterine Cancer

Endometrial cancer is both the most common and the most curable type of gynecologic cancer (Practice Bulletin 2015). Fortunately, among the nearly 55,000 women expected to be diagnosed with endometrial cancer in 2015, most will be diagnosed with early stage disease and given an excellent prognosis. Approximately 67 % of women have localized disease at diagnosis, with estimated 5-year survival at 95 %. Overall 5-year survival for endometrial cancer patients is approximately 82 %, the highest among gynecologic cancers (SEER Stat Fact Sheets – Cancer of the Endometrium). Thus it is important to understand and address the unique needs of this population.

When caring for endometrial cancer survivors, providers must address adverse treatment effects and screen for disease recurrence and second primary cancers. Equally important is addressing cardiovascular health and lifestyle factors. Overall morbidity among endometrial cancer survivors is high, despite favorable cancer prognoses. This has been attributed to the strong association of endometrial cancer with obesity and its related comorbidities including hypertension, diabetes, metabolic syndrome, and pulmonary disease (Von Gruenigen et al. 2006; Bjorge et al. 2010). Women with endometrial cancer are more likely to die from cardiovascular disease than from cancer (Ward et al. 2012), and obesity has been associated with increased morbidity and decreased quality of life in survivors (Courneya et al. 2005; Smits et al. 2014). Recent studies evaluating lifestyle programs that target endometrial cancer survivors have shown that various interventions may be able to increase physical activity levels, improve dietary habits, and influence weight loss in these patients (Basen-Engquist et al. 2014; Von Gruenigen et al. 2008, 2009, 2011, 2012; McCarrol et al. 2014). Further study is needed in this area.

While the majority of women diagnosed with endometrial cancer are postmenopausal, an estimated 25 % are premenopausal. Since 1988, the standard treatment for endometrial cancer has been hysterectomy and bilateral salpingoophorectomy, making loss of ovarian function among premenopausal women treated for endometrial cancer an important issue (Practice Bulletin 2015; Sorosky 2008). These women experience abrupt onset menopausal symptoms, which may exacerbate psychological difficulties and sexual dysfunction.

Traditionally, estrogen replacement therapy in survivors of endometrial cancer has been avoided since most endometrial cancers are estrogen dependent. Review of limited evidence suggests that estrogen replacement may be a reasonable option in premenopausal patients with a history of early stage disease and may be considered with appropriate risk-benefit counseling and oncology consultation (Chapman et al. 1996; Barakat et al. 2006). Of note, some premenopausal

women with endometrial cancer are choosing fertility-preserving or ovarian-preserving therapies (Erkanli and Ayhan 2010; Chaoyang et al.). The details of such treatments are beyond the scope of this review; however, it may influence the future composition of this population.

Furthermore, survivors of endometrial cancer are at increased risk for multiple subsequent cancers, including breast, colorectal, vulvar, vaginal, lung, and urologic cancers. Breast and colon cancers are the most commonly identified second primary cancers in endometrial cancer survivors and require regular screening. Patients with endometrial cancer may have a genetic predisposition for development of other cancers, such as in Lynch syndrome, and should be offered genetic screening when personal or family history indicates (Practice Bulletin 2015; Uccella et al. 2011; Re et al. 1997).

The majority of endometrial cancer recurrences will occur within 3 years of the completion of initial therapy (Fung-Kee-Fung et al. 2006; Salani et al. 2011; Sartori et al. 2010; Tjalma et al. 2004). Approximately 70 % of recurrences are symptomatic (Fung-Kee-Fung et al. 2006; Sartori et al. 2010). Among the asymptomatic recurrences, most are detected by physical exam (Fung-Kee-Fung et al. 2006; Salani et al. 2011; Sartori et al. 2010). The NCCN recommends an exam every 3–6 months for 2–3 years then every 6–12 months. History and physical exam detects up to 100 % of recurrent disease (range 52–100 %) (Sartori et al. 2010; Tjalma et al. 2004).

CA-125 surveillance is optional and imaging should be performed only if clinically indicated according to both the NCCN and SGO (Salani et al. 2011). In patients with low-risk disease, CA-125 levels are only elevated in 0–5 % of recurrences (Fung-Kee-Fung et al. 2006; Tjalma et al. 2004; Rose et al. 1994). Patients with advanced stage or high-grade histologies, however, will have an elevated CA-125 in >50 % of recurrent disease (Rose et al. 1994).

Common practice has been to perform chest X-rays in surveillance. They diagnose up to 20 % of all recurrences (Salani et al. 2011; Tjalma et al. 2004). The more relevant question, however, is if the diagnosis of distant disease will impact survival. Patients with pulmonary metastasis of recurrent uterine cancer have a poor prognosis as systemic chemotherapy is often ineffective. Other imaging modalities such as ultrasound, intravenous pyelogram, and computed tomography (CT) have also shown early detection of asymptomatic recurrences without a survival benefit (Salani et al. 2011; Tjalma et al. 2004). For these reasons, imaging is only indicated in patients with a history or exam concerning for recurrent disease.

Pap smears are not recommended for surveillance of uterine cancer. A restrospective review found that only 2.5 % of all recurrent endometrial cancers were diagnosed with the help of cytology (Tjalma et al. 2004). Other retrospective studies showed only 0.5–0.7 % of endometrial cancer patients had cytology that diagnosed an isolated vaginal recurrence at a cost of approximately $23,487 to $44,049 per recurrence detected (Bristow et al. 2006; Cooper et al. 2006). Additionally, 15 % of patients with biopsy proven vaginal recurrence had a negative pap (Cooper et al. 2006). The opinion of the SGO is that vaginal cytology adds significant healthcare costs without added benefit and that most recurrences at the vaginal cuff can be found on exam (Salani et al. 2011).

Patients with uterine sarcomas may require closer monitoring. An exam every 3 months for 2 years then every 6–12 months is recommended by the NCCN. Additionally, they suggest consideration of CT imaging every 3–6 months for 2–3 years, then every 6 months for the next 2 years, and then annually.

We also recommend routine assessment of psychosocial wellbeing, sexual health, and adverse treatment-related effects, accompanied by treatment or referral as indicated. Furthermore, we recommend medical optimization of cardiovascular health and increased emphasis on healthy lifestyle choices. At minimum, obese endometrial cancer survivors should receive physician counseling regarding weight loss, physical activity, and healthy eating. Ideally, these patients should be referred to weight loss and lifestyle intervention programs available within their

medical communities. Finally, in order to provide optimal care to endometrial cancer survivors, we recommend that these women follow with a gynecologist or gynecologic-oncologist as well as a primary care specialist familiar with the needs of this population.

4.2 Cervical Cancer

Cervical cancer is the third most common gynecologic cancer in the United States. Its incidence has decreased markedly in recent decades with the introduction of widespread screening and treatment of preinvasive disease. The recent introduction of the HPV vaccine will hopefully further decrease cervical cancer incidence in coming decades (American College of Obstetricians and Gynecologists 2013).

Despite improved screening, an estimated 13,000 women are expected to be diagnosed with this malignancy in 2015. Nearly half of these women will be diagnosed with local disease with 5-year survival at 90 %. Overall, 5-year survival among cervical cancer patients is estimated at 68 % (SEER Stat Fact Sheets – Cancer of the Cervix Uteri). Cervical cancer affects younger women when compared with other gynecologic cancers, with mean age at time of diagnosis approximately 50 years, resulting in longer posttreatment life expectancies. In addition, women of lower socioeconomic status and women of minority or immigrant groups are more likely to develop invasive cervical cancer (Ye et al. 2014; Akers et al. 2007).

Women diagnosed with very early stage disease are often treated exclusively with surgery. More advanced disease is generally treated with radiation and chemotherapy. Survivors may suffer from psychosocial difficulties, sexual dysfunction, long-term treatment side effects, and second primary malignancies. Studies have suggested that survivors who received treatment with radiation therapy are at increased risk of suffering from long-term physical effects and sexual dysfunction when compared to those treated with radical surgery alone (Ye et al. 2014; Le Borgne et al. 2013; Harding et al. 2014).

Premenopausal women treated for cervical cancer may suffer from premature ovarian failure as a result of treatment. Estrogen replacement therapy is generally considered to be appropriate in this population and may be considered (Biliatis et al. 2012; Ploch 1987). Women who have not completed childbearing at the time of diagnosis may suffer from psychological and social difficulties resulting from treatment-induced infertility. Fortunately, fertility preservation is increasingly being offered to women with very early stage invasive disease (Abu-Rustum et al. 2008; Pareja et al. 2013; Ramirez et al. 2008), and ovarian-preserving efforts including pretreatment ovarian transposition have been investigated with promising results (Shou et al. 2015; Al-Badawi et al. 2010).

Furthermore, women with a history of cervical cancer are at increased risk of developing subsequent cancers of the vulva, vagina, and rectum as well as tobacco-related malignancies including lung, esophageal, stomach, urogenital, pancreatic, and leukemia in those with a tobacco use history (Balamurugan et al. 2008; Rodriguez et al. 2014; Underwood et al. 2012). Thus, it is important to screen for potential second malignancies and to routinely address tobacco use.

Most recurrences in patients with cervical cancer occur within the first 3 years, with a median of 7–36 months after completion of initial therapy (Elit et al. 2010; Salmal et al. 1998). Patients with isolated local recurrence have improved salvage rates over those with distant disease, so early detection of recurrence can be life-saving. The NCCN-recommended surveillance for cervical cancer includes an exam every 3–6 months for 2 years, then every 6–12 months for 3–5 years, and then annually. They also suggest annual cervical/vaginal cytology and imaging as indicated.

Cytologic evaluation of the vagina/cervix after treatment for cervical cancer is controversial. Though it has been recommended as part of surveillance historically, several retrospective studies have shown that cytology alone is rarely the sole indicator of the presence of disease (Elit et al. 2010; Zanagnolo et al. 2009). One retrospective study calculated that 3,800 pap smears were

performed on 271 patients in order to detect one asymptomatic recurrence (Salmal et al. 1998). SGO recommends elimination of cytologic testing or limiting its use to annually (Salani et al. 2011).

The role of imaging for surveillance of cervical cancer survivors is uncertain. Several studies have shown chest X-ray to detect distant disease in the absence of symptoms in 11–47 % of patients with recurrence (Salmal et al. 1998; Bodurka-Bevers et al. 2000). Most patients with distant metastases are not salvageable so the early detection of chest lesions is unlikely to improve outcomes. PET scans for surveillance, on the other hand, may detect locoregional recurrence when salvage radiation or exenterative surgery is still an option. One retrospective study evaluated PET imaging in asymptomatic women after treatment of cervical cancer. Twelve percent of patients had a positive PET scan 15 months after completion of therapy and another 14 % had a positive scan 21.5 months after treatment. Seven of the 13 patients with asymptomatic disease seen on PET had isolated recurrences amenable to curative therapy. They showed an improvement in 3-year survival over women with symptomatic disease that was not statistically significant (59 vs. 19 %) (Brooks et al. 2009). In another retrospective study, 20 asymptomatic women were found to have recurrence on PET imaging. Eight of these patients had treatment with curative intent and five were cured of disease (Chung et al. 2006). Despite the potential for early detection of recurrence by PET imaging, the cost is high and there is a lack of prospective studies with clear evidence of improvements in outcomes. Radiography is often only employed in patients with a history or exam concerning for disease.

We encourage healthy lifestyle choices and regular tobacco prevention and cessation efforts, including referral to cessation programs for motivated patients. It is important to recognize that many of these patients may suffer from long-term psychological issues or have severe physical effects from cancer treatment. We also recommend educating these survivors on the importance of encouraging their family and community members to undergo routine cervical screening.

4.3 Ovarian Cancer

Ovarian cancer is the second most common gynecologic cancer in the United States, with an estimated 21,000 diagnoses expected in 2015. Significant survival differences exist between women diagnosed with early stage disease and those diagnosed with advanced disease. Unfortunately, 60 % have distant spread at diagnosis and 5-year survival at 28 %. However, women diagnosed with localized or regional spread have better prognoses with 5-year survival at 92 % and 73 %, respectively (SEER Stat Fact Sheets – Cancer of the Ovary; Bhoola and Hoskins 2006).

Ovarian cancer is generally treated with surgery and/or chemotherapy. Survivors may experience neuropathy, cognitive decline, psychosocial difficulties, and sexual dysfunction (Correa et al. 2010; Gutierrez-Gutierrez et al. 2010; Stavraka et al. 2012; Ezendam et al. 2014). Fear of recurrence is of particular concern in this population and may contribute to significant anxiety and decreased quality of life. Studies have shown that psychosocial wellbeing can have the greatest influence on overall quality of life among ovarian cancer survivors (Teng et al. 2014). Adequately powered longitudinal studies are needed to further qualify, quantify, and assess the specific survivorship needs of this population.

When compared to the general population, survivors of ovarian cancer are at greater risk of developing a second malignancy. Since most women treated for ovarian cancer have received a hysterectomy, the risk of a second gynecologic malignancy is less. However, these women are at increased risk of developing a multitude of cancers including breast, colorectal, and bladder cancers. Survivors may carry BRCA1, BRCA2, or HNPCC mutations and should be screened for such based on personal and family histories (Gangi et al. 2014). Patients treated with chemotherapeutic agents such as etoposide and platinum compounds are associated with an increased risk of a secondary leukemia later in life (Kollmannsberger et al. 1998).

Most women who achieve a complete clinical response to initial therapy for ovarian cancer will relapse. Approximately 75 % of these women will

recur, most within 2 years (Gadducci and Cosio 2003; Gadducci et al. 2009). The NCCN guidelines for monitoring for recurrence of ovarian, primary peritoneal, and fallopian tube cancer are for exams with CA-125 (if initially elevated) every 2–4 months for 2 years, then every 3–6 months for 3 years, and then annually after 5 years. They recommend imaging as clinically indicated. Women with borderline tumors or germ cell and sex-cord stromal tumors can have later recurrences, up to 20 years after treatment of the initial disease, and should have annual evaluations beyond 5 years (Salani et al. 2011).

Recently, the monitoring of CA-125 levels during remission has come into question. One randomized controlled trial evaluated the impact of starting therapy for ovarian cancer at the time of biochemical recurrence (Rustin 2010). They randomized 529 women with elevated CA-125 levels to early treatment or to delayed therapy (observation until the patient had clinical or symptomatic relapse of disease). The early treatment group started chemotherapy nearly 5 months earlier and experienced a significant decrease in quality of life compared to those assigned to delayed therapy. The early treatment group demonstrated no improvement in overall survival. Starting chemotherapy earlier in recurrence did not improve outcomes but it did negatively impact patients' quality of life. The dilemma of whether a serum CA-125 should be checked as part of surveillance for ovarian cancer recurrence should be discussed with and individualized for each patient.

Routine imaging for detection of disease recurrence is controversial. There is a paucity of data in the medical literature and no prospective studies to assess this issue. One study retrospectively evaluated patients surveilled with CT imaging every 6 months for 2 years then yearly. In the group of asymptomatic patients with disease found on imaging, 90 % had an optimal secondary cytoreduction compared with 57 % of patients with detection of recurrence based on symptoms. This resulted in an improved overall survival (72 vs. 51 months) compared with women who only had imaging after the onset of symptoms (Tanner et al. 2010). Another retrospective study, on the other hand, found that only 27 % of 331 asymptomatic patients were diagnosed with recurrent disease based on imaging alone and that there was no difference in survival for patients among any of the modalities used to detect recurrence (Gadducci and Cosio 2003; Gadducci et al. 2009). Because of the significant cost of surveillance imaging without any prospective evidence of benefit, imaging is currently reserved for patients with suspected disease recurrence. For patients with symptoms concerning for recurrence, suspicious exam findings or an elevated CA-125, PET-CT scans have been shown in multiple studies to be more sensitive than CT at locating sites of disease. Additionally, PET-CT scans alter treatment in up to 60 % of patients (Bhosale et al. 2010; Fulham et al. 2008; Risum et al. 2009; Thrall et al. 2007). Women who have had fertility-sparing surgery for ovarian cancer represent a special subgroup of patients. If their disease recurs, it is most likely to arise in their remaining gynecologic organs. SGO recommends serial ultrasound in these women every 6 months to evaluate their pelvic organs (Salani et al. 2011).

We recommend screening for neuropathy and cognitive difficulties, psychological and sexual dysfunction, and referral for treatment when indicated. Similar to endometrial cancer survivors, survivors of ovarian cancer benefit from a healthy diet, maintaining supportive relationships, regular physical activity, and maintaining a healthy weight.

4.4 Vulvar/Vaginal Cancer

Vulvar cancer is the fourth most common gynecologic cancer, with approximately 5,000 women expected to be diagnosed in 2015 (SEER Stat Fact Sheets – Cancer of the Vulva). Vulvar cancer diagnoses occur most frequently in women between the ages of 65–75; however, vulvar cancer has increased in younger populations, likely due to increasing HPV prevalence (SEER Stat Fact Sheets – Cancer of the Vulva). As with cervical cancer, the introduction of the HPV vaccine will hopefully decrease vulvar cancer incidence in the coming decades (Balamurugan et al. 2008). Women with vulvar cancer are generally treated

with pelvic surgery and/or radiation therapy (Aerts et al. 2012). Vaginal cancer is considered very rare and often is metastatic from another site or related to HPV.

Overall, the literature assessing survivorship issues specific to vulvar cancer is limited. Patients treated with extensive surgery or radiation therapy seem to be at risk for decreased quality of life, including sexual dysfunction and psychosocial difficulties (Aerts et al. 2012; Gunther et al. 2014; Kunos et al. 2009). These patients may suffer from skin changes including changes in skin texture and color, thickening, contractures, fibrosis, decreased clitoral sensation, and painful intercourse. Patients treated with extensive lymph node surgery or radiation therapy often suffer from chronic lymphedema (Berger et al. 2015).

As vulvar cancer has increased among younger women who often present with less advanced disease, a trend toward less radical surgery has emerged. Wide local excision has been associated with higher quality of life among survivors when compared to radical vulvectomy (Gunther et al. 2014), and sophisticated sentinel node mapping techniques are decreasing the need for radical lymph node surgery and the associated risk of lymphedema (McCann et al. 2015). Overall, more research is needed to define and best meet the evolving needs of vulvar cancer survivors.

Due to the low incidence of vulvar and vaginal cancers, there is a paucity of information to guide surveillance recommendations. There are no guidelines published by NCCN and most strategies are extrapolated from practice patterns for cervical cancer. One report of 330 women with vulvar cancer reported that over 35 % of recurrences or new sites of primary disease were found over 5 years after treatment for their primary cancer (Gonzalez Bosquet et al. 2005). This underscores the importance of long-term follow-up in vulvar cancer survivors. SGO recommends regular and long-term examinations of the vulvar, vaginal, cervical, and perianal tissue as well as assessment of the inguinal lymph nodes (Salani et al. 2011). Routine imaging is not recommended.

Continue with routine guideline-recommended screening for other cancers. In tobacco users we recommend an emphasis on cessation. Finally, we recommend approaching these patients with awareness that mental health or sexual counseling may be indicated, especially in patients with a history of extensive pelvic surgery or radiation therapy.

4.5 Gestational Trophoblastic Neoplasia

GTN is a rare malignant lesion arising from placental trophoblastic tissue. It encompasses invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. Occurring in approximately 1: 40,000 pregnancies worldwide; it is most common in Asia. The majority of GTN is cured with chemotherapy, leaving relatively young survivors with concerns including long-term consequences of therapy, reproductive concerns, and concerns of recurrent disease.

Given that GTN is a tumor of women of reproductive age, concerns about future fertility is very important to this population. In women with a history of molar pregnancy, there is an approximately 1 % risk of repeat molar pregnancy and this should be considered by the obstetrician-gynecologist seeing these patients. If treated with fertility-sparing treatment methods, which is common for these diseases, the majority of research looking at reproductive outcomes show pregnancy outcomes that are similar to the general population with a live birth rate of approximately 70 % without increased risk of anomaly. However, it is important to note that women who have received chemotherapy for GTN have a slightly increased risk of stillbirth of approximately 1.3 % and should be carefully monitored in later pregnancy (Gadducci et al. 2015; Vargas et al. 2014).

Other matters of concern involving these patients include need for contraception. Use of contraception, including hormonal contraception, is encouraged, especially during initial surveillance of GTN. Preventing pregnancy during this time is important as a pregnancy will alter the bHCG and may mask persistent disease. This

should be managed with the aid of the treating oncologist. In addition, women who have received certain chemotherapies, especially platinum compounds, have an increased risk of secondary leukemia.

5 Conclusion

The number of gynecologic cancer survivors is expected to continue to increase in coming decades. While further research is warranted to better understand and meet the needs of this population, there are many things that the general gynecologists can do to manage the survivorship care of these women. Attention to the unique psychosocial symptoms, treatment-related sequella, cancer type specific issues, and management of general health maintenance and other health issues would improve the health and quality of life of gynecologic cancer survivors.

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Fertility Sparing Treatment for Ovarian Cancer

Katherine Nixon and Christina Fotopoulou

Contents

Abstract

Consideration of fertility sparing options in the management of ovarian cancer is an increasing concern for gynecological oncologists. For various reasons, women are continuing to delay having children until later years when they may be more at risk of developing ovarian cancer. Preserving fertility in the presence of ovarian cancer diagnosis is a difficult scenario for all involved and creates a balancing act between patients' sometimes desperate wishes and maintaining safe clinical practice. There is obvious difficulty in researching the impact of fertility sparing surgery and alternative treatments for ovarian cancer, as a prospective analysis would be unethical; however, retrospective reviews of cases have been performed to aid guidelines regarding safest management options. We will consider the options available to patients who wish to preserve their fertility and the international guidance depending on types of cancer and method of treatment.

Keywords

Ovarian Cancer • Fertility • Stage • Prognosis • Reproduction

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1 Introduction

Annually in the UK, around 500 women under the age of 45 are diagnosed with ovarian cancer. Many of these women will be wishing to preserve their fertility potential and will need careful counseling regarding this. Approach to these, as with all gynecological oncology cases, should be with a multidisciplinary team. Being diagnosed with ovarian cancer at any stage of life is an extremely distressing situation for patients, but for younger women, adding in the possibility of losing the ability to conceive has the potential to make it much more devastating. The possibility of losing fertility potential as a result of ovarian cancer treatment has been shown to have a negative effect on quality of life for those patients who survive the disease (Duncan et al. 2011).

Management plans for patients with ovarian cancer are decided by teams of gynecological and medical oncologists with guidance from radiologists and pathologists. Most ovarian cancers will require surgery of some kind with the possibility of adjuvant chemotherapy, usually platinum based. Both the surgery and the chemotherapy have the potential to take away a patient's fertility. Surgery will usually involve removal of the affected ovary/tube, often with the necessity or advice of completion of staging by removing the uterus, contralateral tube plus other biopsies from around the abdomen, depending on the stage and grade of the cancer.

The stage and grade of the cancer are the most important factors guiding management advice, with early stage, low grade types proving to be more favorable for fertility sparing management options than high grade/stage. Retrospective trials that have been conducted show that fertility sparing surgery can represent a realistic alternative to the more traditional radical cytoreductive approach in women of child bearing age with early stage disease, without compromise to prognosis.

It is important that we clearly differentiate between the types of ovarian cancer when discussing surgical options. We know more about the potential impact on prognosis of fertility preserving surgery in early stage borderline, germ cell, and granulosa cell tumors (Fotopoulou et al. 2009). Epithelial ovarian cancers are more of a gray area; however, with greater understanding and surgical expertise less radical practices are being used for early stage disease.

2 Surgical Management

There are different treatment approaches depending on the type of ovarian cancer diagnosed. Long standing evidence exists for good outcomes with conservative surgical management for early stage borderline, germ cell, and granulosa cell tumors. These cancers tend to follow predictable courses of progression. Preservation of fertility can be offered without compromising treatment of the disease, with 5-year survival rates of around 90 % and no alteration in relapse rates. Fertility outcomes, measured by rates of conceptions and live births, have been good in these cases, both following surgery only management and also after chemotherapy regimes.

Clinical progression with epithelial ovarian cancer, the most common histological type, varies vastly with high levels of relapse. Therefore, conservative, potentially fertility sparing management regimes are adopted less frequently because of the concern over a poorer outcome. The diversity of presentation, spread, and relapse is attributed to the widespread intratumoral heterogeneity within these cancers. Despite great leaps in understanding the etiology of the disease over the last 20 years, prognosis has remained fairly constant. Due to concerns over endangering patients' lives by using more conservative measures, this approach is not one readily adopted by the specialty.

In terms of decisions based on staging, current international guidelines would not recommend fertility sparing techniques for ovarian cancer including and above stage II as defined by the International Federation of Gynecology Oncology (FIGO), as from this classification the disease has spread beyond the boundaries of the ovaries (Helm and Harris 2015). Furthermore, by FIGO

staging, any ovarian cancers apart from stages Ia, Ic1, and Ic3 involve both ovaries or the surface of the affected ovary/tube and therefore these would not be suitable for a more conservative approach. There is limited data on outcomes of cases where macroscopic tumor deposits have been left in situ at the time of surgery in order to preserve fertility. Although still incredibly difficult, clinicians may find counseling for these higher stage cases relatively more straightforward as there are limited options, and guidance would generally be to opt for maximal cytoreductive surgery including bilateral salpingoophorectomy, hysterectomy, and following with adjuvant chemotherapy. Counseling, where fertility sparing surgery may be a safe option, can be more problematic as patients and their partners/families will have more considerations to take on board.

For stages 1a and 1c, it is less clear what the best course of treatment should be. Fertility sparing surgery requires leaving one ovary, tube, and the uterus in situ. There will always be concern regarding the chance of disease being present in these sites that is not visible macroscopically and about the risk of recurrence if they are not removed. To leave these structures in situ involves macroscopically staging the disease at the time of surgery and determining that the contralateral ovary/tube appear normal and there is no evidence of disease elsewhere. To aide staging, biopsies can be taken at the time of surgery from the pelvic and abdominal peritoneum, the omentum and lymph nodes, (the most common sites of dissemination). However without the resection of the contralateral ovary and tube staging is not complete (Mangili et al. 2011). New techniques are being adopted involving peritoneal resection from the pelvis and uterine serosa to aid staging (Rasool and Rose 2010). Uncertainty exists around the best management of Ic disease. This is regarding whether there is a difference between outcomes of patients who have had surgical spill of their disease from cyst rupture (Ic1) or those who have malignant cells present in peritoneal washings or ascites already before surgery, without evidence of other disease (Ic3).

The histological grade is also important in determining if fertility sparing is a safe option. In general, high grade, poorly differentiated, or clear cell histological cell types, irrespective of stage, are not deemed suitable for fertility sparing surgical techniques. Current evidence suggests that in stage 1a, low grade i.e., moderately or well-differentiated nonclear cell histology, it is appropriate to perform fertility sparing surgery without compromising the oncological outcome (Kajiyama et al. 2011). These patients may also not require adjuvant chemotherapy. There is an apparent discrepancy between stage 1c with surgical spill and those with noniatrogenic positive peritoneal cytology. Iatrogenic cases show better outcomes with fewer relapses and therefore a conservative course of action is not recommended for cases with preexisting malignant cells in ascites or peritoneal washings.

Average relapse rates in those undergoing fertility sparing surgery have been shown to be around 10 % (Fotopoulou et al. 2012). While there is no significant difference in relapse rates between cases of stage 1a or 1c disease, the higher proportion of relapses tend to be in those with 1c or higher grade disease. Research has shown that in cases of low stage disease where fertility is not an issue and bilateral salpingoophorectomy has occurred, in order to complete staging, there is a low rate of tumor invasion in the contralateral ovary. This evidence supports the opinion for surgeons being capable of determining macroscopically if an ovary contains tumor at the time of surgery and therefore visually staging the disease; however, without biopsy this diagnostic strategy is not watertight.

International guidelines now recommend that a fertility sparing surgical approach is appropriate in cases of stage 1a or 1c1 low grade cases following discussion with the patient and fully informed consent.

3 Chemotherapy

Of the cases where fertility sparing surgery is deemed appropriate, those with stage Ia/Ic1 clear cell carcinoma or stage Ic3 are recommended to have adjuvant chemotherapy. Platinum-based chemotherapy agents are widely used in ovarian cancer and have the potential to cause ovarian

failure and induce early menopause; this is more typical in older patients who may have been already approaching menopausal age. However studies have shown that the majority of patients, around 95 %, receiving chemotherapy return to their normal menstrual cycle 6 months to a year following the end of their treatment (Satoh et al. 2010). Use of agents such as gonadotropin releasing hormone (GnRH) analogues or combined oral contraceptive pills (COCP) during chemotherapy have been investigated (Del Mastro et al. 2014). The aim of these medications is to downregulate the ovary during the treatment course and thus hope to reduce the toxic effect of the chemotherapy on the ovarian cells. This has been shown to be affective in some cases; however; there is insufficient conclusive data and no statistical significance has been demonstrated, hence use is still debated. Most of the research into this area has been performed in hematological and breast cancers and so understanding of its potential application to ovarian cancer management is limited.

Other options for fertility are cryopreservation of part of the ovary or oocytes; however, there is always a possible risk with this that part of the preserved tissue may contain malignant cells. Pregnancy rates following cryopreservation are reportedly low, and with this and the possibility of malignancy in the tissue, it is not a commonly used option.

4 Reproductive Outcomes

Both surgical management and chemotherapy treatment have the potential to affect fertility. Despite this, rates of successful conception following fertility sparing treatment have been good, reportedly around 66–100 % in those who actively try to conceive. A minority of patients appear to require fertility assistance following treatment. There does not appear to be evidence of an increase in adverse pregnancy outcomes such as miscarriage, preterm labor, or congenital malformations in those who have undergone treatment. This information should be communicated to patients deemed suitable for fertility sparing measures to help with counseling and decision making.

5 Conclusion

Ovarian cancer has a huge impact on a patient's life no matter at what age the diagnosis is made. As society changes and women chose to have children at a later age, diagnoses and decisions on management are going to be increasingly difficult. Management regimes may seem more controversial in attempts to preserve fertility for those younger patients where this is a concern. There is well-acknowledged evidence of fertility preserving techniques in granulosa cell, germ cell, and borderline tumors without compromise in outcome. In the case of epithelial ovarian cancer, fertility sparing surgery is a reasonable course of action for those with stage 1a or 1c1 with low grade nonclear cell disease with no evidence of an impact on relapse rates or overall survival. Chemotherapy treatment used in ovarian cancer can lead to premature ovarian failure. In the majority of cases, however, ovarian function and menstruation will return to normal after the termination of treatment. In those aiming to conceive following the completion of treatment, rates of pregnancy and pregnancy outcomes are similar to a nonovarian cancer population. Careful counseling is required and all available facts should be given to the patient. This will enable them to make an informed decision regarding treatment options prior to commencement in cases where fertility sparing surgery is deemed appropriate. Gynecological oncologists have the responsibility to both adequately and safely treat the disease whilst also bearing in mind the patients' wishes for fertility preservation in ovarian cancer.

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Anatomy of the Female Genital System

Dalal Eldick and Fausto Andrade

Contents

Abstract

Female pelvic anatomy requires a great deal of comprehensive knowledge that can often seem unattainable. This chapter focuses on the basics of this arena into thirteen sections that may be easier to understand once separated. These 13 sections will cover the uterus, adnexa, and vulvar organs as well as the pelvic bones, vessels, and innervation. With the addition of specific and important surrounding structures and planes, there is emphasis on clinical and surgical application. This information is geared toward a better understanding of the female anatomy for the gynecologist, internist, and family physician, but it is particularly directed to the pelvic surgeon performing laparotomy and/or laparoscopy within this area.

Keywords

Female pelvic anatomy • Pelvis • Gynecology • Surgical gynecology

1 Introduction

The word "gynecology" was first used in the middle of the nineteenth century. Gynecological anatomy was first explored in Alexandria by the Roman physician, Soranus. Soranus was interested in the disease of women and children, and one of his most important textbooks was named *Gynecology*. He focused his textbook on normal and abnormal anatomy, care of the newborn, and

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care of abnormal pregnancy but is particularly remembered for describing the anatomy of the anatomy of the gravid uterus. It was the Hungarian obstetrician, Dr. Ignaz Semmelweis, who pioneered the way with the importance of hygiene in preventing postsurgical sepsis. Two fathers in the world of surgical gynecology that need recognition are Dr. Ephraim McDowell who performed the first ovarian cystectomy and Dr. James Marion Sims who performed the first vesicovaginal fistula repair. These are the leaders that paved the way for a modern understanding of gynecological anatomy in the nongravid woman and the techniques of surgical repair.

It is interesting that the first recorded surgery in history is a cesarean section but that there is a fairly contemporary understanding of gynecological anatomy. This dichotomy can be better understood by the words of medical historian Howard Kelly when he stated "the history of gynecology seems to me more full of dramatic interest than the evolution of any other medical or surgical specialty." However, before understanding the gravid state or the pathology that can affect this system, it is important to know the foundation of its anatomy. This chapter is divided into thirteen sections. The anatomy of the female genital system including the uterus, adnexa, and vulva along with the blood vessels, lymphatics and nervous system is addressed below (Baggish 2011; Howard and Rock 2015).

2 Genital Structures

1. **Vagina**
   - The vagina is a flexible viscus that is shaped by its surrounding structures and its attachments to its adjacent walls.
   - The vagina is bent at a 120° angle at the distal one third and proximal two third junction at the level of levator ani attachment. It is typically 7–9 cm in length with the anterior wall typically shorter by 3 cm than the posterior wall as this is where the cervix lies. But these dimensions vary between individuals.
   - The vagina's anatomical relations can be best understood by dividing it into thirds. The distal one third is fused anteriorly with the urethra and posteriorly with the perineal body and laterally to the levator ani by the fibers of Luschka. The mid one third portion of the vagina is comprised of the vesicle neck and trigone anteriorly, the rectum posteriorly, and the levators laterally. The proximal one third of the vagina is adjacent to the bladder and ureters anteriorly, posteriorly to the cul-de-sac, and laterally to the cardinal ligaments.
   - The wall of the vagina is compromised of the same layers of all hollow viscera which include the mucosa, submucosa, muscularis, and adventitia. This holds true for all parts of the vagina excluding the segment covered by the cul-de-sac which contains no serosal layer. The vaginal mucosa is nonkeratinized squamous epithelium. The submucosa is a dense, dermis-like layer and is fused with the muscularis in a bihelical arrangement. Outside the muscularis is the adventitia which is the connective tissue labeled "endopelvic fascia."
2. **Uterus**
   A. **The Uterine Corpus**
      - The uterus is a fibromuscular organ that varies in shape and size according to the amount of estrogen stimulation and previous parity. It is divided into two parts: the upper muscular corpus and the lower, fibrous cervix. The corpus is generally much larger than the cervix in women of reproductive age. However, in prepubescent girls and menopausal women, the sizes of both these structures are more equal.
      - The uterus is divided into three layers: the endometrium, a surrounding thick muscular wall called the myometrium, and the top layer called the serosa. The endometrial cavity is triangular in shape. The top of the endometrial cavity is called the

fundus. The endometrium is comprised of glandular columnar epithelium and specialized stroma. The myometrium is the thickest part of the uterus and is comprised of smooth muscle. The serosa consists of the visceral peritoneum

B. **The Uterine Cervix**

- The cervix is a tubular structure that serves as a channel between the vagina and uterine corpus. It is comprised of two portions: the portio vaginalis which protrudes into the vagina and the superior portion called the portio supravaginalis that is above the vagina but below the corpus. The portio vaginalis is made up of nonkeratinized squamous epithelium. Its endocervical canal is made up of columnar mucus-secreting epithelium.
- The proximal border of the cervical canal is defined by the internal os that opens into the endometrial cavity. The distal border is defined by the external os that incorporates the squamous epithelium of the portio vaginalis and the glandular epithelium of the endocervical canal. This squamocolumnar junction is termed the "transition zone" and is particularly subject to malignant transformation.
- The cervix is covered laterally by the broad ligament and anteriorly by the bladder and posteriorly serves as the anterior boundary of the posterior cul-de-sac (pouch of Douglas). The posterior segment of the cervix is the only part that has a serosal covering.

3. **Adenexal Structures**

A. **The Fallopian Tubes**

- The fallopian tubes are paired tubular structures that serve as highways between the ovaries and uterus. They typically range 7–12 cm in length. Each tube is divided into four parts. The portions include the interstitium, where the tube passes through the uterine cornu, the isthmus that is the narrowest segment of the tube comprised of a thin lumen and a thick muscular wall, the ampulla that contains an expanding lumen and muscular folds, and the infundibulum located at the end of the tube forming smooth muscle projections to increase the surface area for facilitating ovulated ova pick-up. The lumen of the fallopian tube thus connects the uterine cavity to the abdominal cavity.
- The inner layer of the fallopian tube, the internal mucosa (endosalpinx), is comprised of three types of columnar epithelium: secretary, ciliated, and peg cells. The endosalpinx is arranged in folds that increase in number toward the fimbria.
- The middle muscular layer (myosalpinx) of the fallopian tube is composed of an outer layer of longitudinal smooth muscle fibers and an inner circular layer. A third layer is added in the interstitial portion.
- The outermost layer of the fallopian tube, the serosa, is composed of an epithelial layer that is histologically the same as peritoneal cells. The mesosalpinx is part of the broad ligament that stretches from the ovary and wraps round the fallopian tube forming the serosal layers.

B. **The Ovaries**

- The ovary is suspended laterally to the pelvic wall by the infundibulopelvic (IP) ligament. The IP contains the ovarian artery and vein. The ovary is connected medially to the uterus by the utero-ovarian ligament. It measures about 2.5–5 cm long, 1.5–3 cm thick, and 0.7–1.5 cm wide depending on its activity or suppression during reproductive life.
- The ovary's external epithelial layer is composed of cuboidal germinal cells. For ovulation, this layer is ruptured. Beneath this layer is a layer of dense

connective tissue, the tunica albuginea. The external layer or ovarian cortex contains ovarian follicles with stroma between them. The cortex also contains corpora lutea and corpora albicantia.

- The innermost layer is the ovarian medulla. The medulla is fibromuscular with many blood vessels and connective tissue.
- The mesentery of the ovary is called the mesovarium. The mesovarium is the portion of the broad ligament that reflects onto and holds the ovary in place. The mesovarium does not cover the ovary.
- The round ligaments extend from the uterus laterally and are a homolog of the gubernaculum testis. After moving laterally from the deep inferior epigastric vessels, they become rounded and enter through the inguinal canal to the subcutaneous tissue of the labia majora. The mesentery of the round ligament and uterus is called the mesometrium.

The ovaries and fallopian tubes form the adnexa.

4. **Support Structures**
   - The parametrium is composed of the fibrous tissues that connects to the uterus and separate the supravaginal portion of the cervix from the bladder. The parametrium extends laterally between the two layers of the broad ligament. The uterosacral and cardinal ligaments form the medial and lateral borders of the parametrium. These ligaments extend laterally from the cervix to the pelvic wall. These ligaments form the suspensory tissues that hold the cervix posteriorly in a position over the levator plate of the pelvic diaphragm.
   - The uterosacral ligament marginates the cul-de-sac of Douglas. It is formed by a combination of smooth muscle, autonomic nerves, connective tissues, and blood vessels. The uterosacral ligament extends from the posterior base of the uterus to the anterior sacrum.
   - The cardinal ligament attaches at the isthmus above the cervix and attaches to the pelvic wall over the piriformis muscle in the greater sciatic foramen. The cardinal ligament provides support for the uterus, cervix, and upper portion of the vagina, whereas the uterosacral ligament only provides support for the uterus and cervix.
5. **Blood Supply**
   - The aorta provides the blood supply to the pelvic structures through both the iliac branches and the ovarian artery. The aorta bifurcates at spinal level L4–L5 into the right and left common iliac arteries. The common iliac arteries are only about 4 cm long as they run along the psoas muscles and bifurcate at the pelvic brim forming the external and internal (hypogastric) iliac arteries. The internal iliac artery is the main blood supply to the pelvic organs. The branches of the iliac artery are variable but include the uterine, vaginal, obturator, inferior vesical, middle rectal, and internal pudendal arteries:
     - The uterine artery enters the uterus at the junction of the corpus and cervix and rises laterally. It also flows into the marginal artery on the side of the uterus and thus is able to provide upward and downward flow to the uterus.
     - The vagina receives its blood supply from the uterine artery and the vaginal branch of the internal iliac artery, and they anastomose at 3 o'clock and 9 o'clock positions of the vagina. The distal vagina also receives blood from the pudendal and hemorrhoidal vessels.
     - Bifurcation of the internal and external iliac blood vessels occurs within the sacroiliac joint. Before descending under the inguinal ligament, the external iliacs give form to the deep circumflex and deep inferior epigastric vessels. The internal iliac artery supplies the pelvic structures and splits

into anterior and posterior divisions about 3–4 cm after leaving the common iliac artery. The posterior division is comprised of the iliolumbar, lateral sacral, and superior gluteal vessels that supply the pelvic wall and gluteal region. The anterior division is comprised of the obturator, internal pudendal, and inferior gluteal branches that supply pelvic muscles; the uterine, superior vesicle, inferior vesicle (vaginal), and middle rectal supply pelvic organs. Ligation of the internal iliac artery is helpful in the management of postpartum hemorrhage.

- The adnexa blood supply consists of the ovarian artery, which is a branch of the aorta just below the renal artery. The venous plexus drain into the vena cava on the right and the renal vein on the left. The ovarian artery and vein also pass along the ovarian mesentery to connect with the upper part of the marginal artery of the uterus.

6. **Innervation**
   - Many of the pelvic structures are innervated by nerves originating from the sacral plexus, coccygeal plexus, and pelvic autonomic nerves:
     - The sacral plexus (innervated by the 4–5th lumbar spinal nerves) runs down the posterior pelvic wall anterior to the piriformis muscle. The nerves that form from the sacral plexus include pudendal nerves (clitoris), perforating cutaneous and posterior femoral cutaneous nerves, pelvic splanchnic nerves, sciatic nerve, superior and inferior gluteal nerves, as well as the nerve to the obturator internus, piriformis, and quadratus femoris muscles.
     - Coccygeal nerves (formed by the 4th and 5th sacral spinal nerves) innervate the coccygeus and levator ani muscles and that sacrococcygeal joint.
     - Pelvic autonomic nerves control blood flow, peristalsis, contraction of the bladder and rectum, and hormone levels. They include sacral sympathetic trunks, superior hypogastric plexus, inferior hypogastric plexuses, and pelvic splanchnic nerves.
   - The ovaries and fallopian tubes are innervated by the T10–11 renal plexus and the parasympathetics of the vagus nerve.
   - The superior hypogastric plexus (L1–2) receives input from the splanchnic nerves and afferent pain input from the pelvic viscera. Parasympathetic input derives from S2 to S4.
   - The inferior hypogastric plexus (L2–5) is comprised of three parts: vesical plexus, uterovaginal plexus, and middle rectal plexus. It can be affected during parametrial tissue dissection during hysterectomies and cause postoperative voiding dysfunction and urinary retention.
   - The uterus receives nerve innervation via the uretovaginal plexus called Frankenhauser ganglion. This plexus lies medical to the medial to the uterine vessels and lateral to the uterosacral ligament and receives sympathetic input from T10 to L1 and parasympathetic input from S2 to S4. Its caudal fibers also innervate the vestibule.
   - During surgery it is important to be cognizant of nerves that may be injured. Retraction during laparotomy can cause injury to the genitofemoral branch of the lumbosacral plexus (L1–L2), leading to anesthesia to the lateral labia and medial thigh. Retraction or hyperflexion of the hip while in lithotomy position can cause injury to the femoral cutaneous nerve (L2–L3), leading to anesthesia or abnormal sensation to the anterior thigh.
7. **Lymphatics**
   - Most of the lymph nodes of the pelvis follow the corresponding blood vessels.
   - The ovaries drain into the para-aortic lymph nodes. During dissection, the boundaries are the following: superiorly includes the origin of the inferior mesenteric artery, inferiorly is the midportion of the common iliac and laterally bordered by the ureters.

- Lymph drainage from the uterus flows in the direction of its attachments, starting with the cardinal, uterosacral, and eventually round ligaments. These drain into internal iliac nodes.
- Within the pelvis, lymph node chains can be divided into external iliac, internal iliac, common iliac, medial sacral, and pararectal nodes. The medial and pararectal nodes are rarely involved in gynecological diseases.
- External iliac nodes receive drainage from the inguinal nodes from the leg.
- Internal iliac nodes drain the pelvic viscera, and most of these nodes lie in adipose along the lateral pelvic wall.
- The upper two thirds of the vagina and bladder drain into the uterine lymphatics into the internal iliac lymph nodes. The lower one third of the vagina and distal urethra drain into the inguinal nodes.

8. **The Ureter**
   - The ureter is medial to the ovarian vessels when it crosses over the bifurcation of the internal and external iliac arteries entering the pelvic brim. Upon entering the pelvis, it lies in connective tissue attached to the peritoneum of the lateral pelvic wall and medial leaf of the broad ligament. It then passes under the uterine artery at 1.5 cm lateral to the cervix. It then lies on the anterior wall of the vagina where the cervix is detached during a hysterectomy.
9. **The Vulva and Erectile Structures**
   - The bony outlet of the pelvis is bordered by the ischiopubic rami anteriorly and the coccyx and sacrotuberous ligaments posteriorly and divided into anterior and posterior triangles. These triangles share a base between the ischial tuberosities. The layers of the anterior triangle mimic that of the abdominal wall. The superficial layer is composed of the vulva, overlying the fascial layer that is the perineal membrane and deep to that is the muscular layer comprised of the levator ani muscles.
   - The structures of the vulva consist of the mons, labia, clitoris, vestibule, and associated erectile structures. The mons lies on the pubic bone in a layer of adipose and hair-covered skin. Posteriorly from the mons lies the labia majora which also shares the same hair-covered skin. The labia minora, vestibule, and glans clitoris lie between the labia majora. The labia minora are skin folds that split anteriorly over the clitoris.
   - The vestibule is the area between the labia minora, where the urethral introits and vaginal introituses are located. The hymenal membrane is a ring that surrounds the vaginal orifice. The ducts of the bartholin's glands are located posterior laterally of the vestibule at 4 o'clock and 8 o'clock. The ducts of the Skene's glands are located laterally of the urethra within the vestibule. Blockage of these ducts can cause cysts or abscesses.
   - The pudendal nerve (S2–S4) supplies sensory and motor innervation to perineum. The blood supply originates from the pudendal artery. The nerve and artery are differentiated into three branches: the clitoral, perineal, and inferior hemorrhoidal.
10. **The Pelvic Bones**
    - In order to assume an upright position, without pelvic organs descending out through the abdominopelvic cavity, a support system is crucial. This system is called the pelvic floor and consists of the levator ani muscles and perineal membrane.
    - The perineal membrane, formally called the urogenital diaphragm, forms the inferior portion of the anterior pelvic floor. It provides support to the posterior vagina by forming the attachment between it and the perineal body and then from perineal body to the ischiopubic rami. It can be torn during parturition and that can result in abnormal descent of the pelvic floor.

- Cephalad to the perineal membrane are the compressor urethral and urethral vaginal sphincter that help the two urethral sphincter muscles to compress the distal ureter. It is controlled by a branch of the pudendal nerve.
- The perineum is the genital skin between the thighs including the external genitalia and anus. The perineal body consists of the lower vagina and skin of the perineum and anus.
- The ischiorectal fossa forms the posterior triangle of the pelvis and lies between the levator ani muscles (they lie medially and superior) and the obturator internus muscle (lies laterally). It contains the external anal sphincter and the pudendal neurovascular trunk.
- The external anal sphincter is attached to the coccyx posteriorly and attaches fibers to the perineal body superiorly. The internal anal sphincter is a smooth muscle that can be torn during labor and delivery (fourth degree laceration).
- The levator ani muscles are composed of the pubococcygeus, puborectalis, and iliococcygeus muscles. The medial area that contains the openings of the urethra, vagina and rectum is called the urogenital hiatus. The sling of anterior support for this area is formed by the pubococcygeal and puborectal muscles. The posterior portion of support is formed by the iliococcygeus muscle.

11. **Pelvic Bones and Ligaments**
    - The bones of the pelvis are comprised of the ilium, ischium, pubis, sacrum, and coccyx.
    - In a standing woman, the anterior superior iliac spines (ASIS) and front of the pubic symphysis are in the same plane, perpendicular to the floor, tilting the pelvic inlet anteriorly and making the urogenital hiatus and ischiopubic rami parallel to the ground.
    - The ischial spines can be palpated vaginally and rectally and serve as a point of fixation for pelvic support structures such as levator ani muscles and sacrospinous ligament. The ischial spine is also palpated to determine fetal station during labor.
    - Beneath the pubic symphysis, two pubic bones form the pubic arch which can vary between 44 and 110° (mean angle is 75°). The pubic arch in men is generally 50–60° and that of women is around 70–90°. A narrow pubic arch can result in dystocia during labor and delivery.
    - The pubic symphysis normally has a 4–5 mm gap, but it has increased mobility during pregnancy. It can become abnormally separated during childbirth called pubic diastasis. Greater than a 2 cm gap requires surgical intervention.
    - The sacrospinous ligament is a strong, triangular shaped ligament that divides the lateral pelvic outlet into the greater and lesser sciatic foramen. It is an attachment point for the vaginal apex in the treatment of vaginal prolapse.
    - The sacrotuberous ligament is also triangular shaped and forms the inferior lateral border of the lesser sciatic foramen. The apex is attached to the medial ischial tuberosity.
12. **Avascular Planes**
    - The anterior cul-de-sac, also known as the vesicouterine pouch, is the space that separates the uterus from the dome of the bladder. During hysterectomy the vesicouterine peritoneal fold is dissected off the bladder to enter the vesicovaginal space.
    - The posterior cul-de-sac, also known as the pouch of Douglas or rectouterine pouch, is the space between the uterus and rectum.
    - The prevesical space of Retzius separates the bony pelvis and rectus muscles. It is bounded dorsally by the proximal urethra and bladder.
    - The rectovaginal space is located dorsally to the vagina and it begins at the apex of the perineal body. The lower urinary and

lower genital tracts are separated by the vesicovaginal space and vesicocervical space.

3 Cross-References

- Abdominal Hysterectomy: Indications, Avoiding Complications
- Benign Vulvar and Vaginal Pathology
- Laparoscopic Hysterectomy
- Management of Intraepithelial Lesions of the Cervix
- Management of Intraepithelial Lesions of the Cervix
- Operative Hysteroscopy
- Pelvic Organ Prolapse: Diagnosis, Treatment, Avoiding Complications
- Vaginal Hysterectomy: Indications, Avoiding Complications

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Gynecologic History and Examination of the Patient

Alejandra Salazar and Fausto F. Andrade

Abstract

Gynecologists are primary care providers for women. It is very important that a complete, comprehensive history and physical examination are performed and that every aspect of the patient's health is addressed during the gynecologic visit. The patient interview should include gynecologic and obstetrical histories, as well as past medical, surgical, family, and social history. Once an overview of the patient's health history is completed, focus can then be turned into specific complaints. In gynecology, these often are vaginal complaints, abnormal uterine bleeding, contraception counseling, fertility issues, urinary incontinence and prolapse, menopausal symptoms, or problems during intercourse. Attention should be also placed on complaints that can be associated with increased risk for gynecologic malignancies. Physical exam will then complete the encounter. The exam is focused on the patient's chief complaint but should also include a general overview. At this time, appropriate screening testing can be performed and specific issues addressed. The goal of the gynecologic visit is to address all of the woman's concerns, to obtain significant information that will guide diagnostic testing and treatment recommendations, and to develop a relationship between the practitioner and patient that will benefit the patient's health status and future well-being.

Keywords

Interview • Medical history • Gynecological history • Abnormal bleeding • Vaginal discharge • Physical examination • Pelvic examination • Speculum examination • Pap smear • Sexually transmitted diseases • Well woman exam • Gynecologic exam

Contents

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1 Introduction

Every woman at some point in her life will have a gynecologic complaint. With the passing of time, gynecologists have become primary health providers, available for firsthand general healthcare. As women usually go to the gynecologist every year, it is important that a good relationship is established between the patient and the healthcare provider with a level of trust that will allow for a complete and effective history and physical examination. Traditionally, women visit the gynecologist when it is time for their Pap smear testing. In recent years, early establishment of gynecologic care before a Pap smear is needed and has been encouraged, as women become sexually active earlier, and there are many bleeding problems that can arise after menarche and during puberty. Today, women are encouraged to have their first gynecologic appointment at around age 13–15. This visit will be the most important and will create an impression that the patient will carry for the future.

Accurate and complete history and physical examination are the most important tools in screening, diagnosis, and counseling that are performed by a healthcare provider. A detailed review of a patient's health status, previous medical conditions, and gynecologic history provides pertinent and important information that guides the physical and pelvic examination, furnishes the indications for screening, and directs the selection of diagnostic testing and imaging studies needed to arrive at a correct diagnosis and treatment plan. Care of each patient should be individualized and tailored to each woman's specific needs. Every aspect of the history and physical examination that should be addressed in the initial visit as well as the most common complaints seen in a gynecologic visit is outlined in this chapter. The goal of the physician-patient encounter is to provide a safe environment in which the patient can be honest and open and to ensure that all her concerns are addressed appropriately. After requisite knowledge of the patient is obtained, diagnostic and treatment recommendations can be made with confidence.

2 History

Learning about a person's medical history can aid the physician in coming up not only with a differential diagnosis for the presenting complaint but it may also discover other abnormalities that need further investigation. It is very important, as a clinician, to take relevant but at the same time complete histories that are complementary to the patient's chief complaint. In gynecology, there are several topics that particularly need to be addressed.

2.1 Gynecologic History

Components of a complete gynecologic history generally first include bleeding history:

- For premenopausal women, age of menarche, frequency, regularity, and length of the menstrual period are documented. It is important to address amount of flow as well, the number of pads used per day, and the occurrence of intermenstrual bleeding. Amenorrhea, irregular periods, dysmenorrhea (painful periods), and menorrhagia (heavy periods) may signal ovulatory dysfunction, structural abnormalities, or endocrine problems. All this information allows the practitioner to interpret these patterns based on the female's age and comorbidities and to determine which problems can be easily managed (NSAIDs or OCPs) or those that may be more serious and require immediate attention (bleeding disorders, Müllerian disorders).
- Once the female is over 35 or perimenopausal, the pattern and frequency of bleeding may direct the provider toward performing

endometrial sampling to rule out hyperplasia or cancer diagnosis. For postmenopausal women, the occurrence of unexplained bleeding generally requires endometrial sampling.

The next part of the gynecologic history involves questions related to sexual intercourse. At this time in the interview, it is vital that the patient is comfortable with the interviewer so responses are accurate and detailed:

- For younger, reproductive-aged patient, information on coitarche, as well as number of sexual partners currently and in the last year, is documented. Contraceptive history, present use, side effects, reasons for discontinuation, as well as condoms for STD protection are also important information.
- For perimenopausal and postmenopausal women, emphasis is placed more on problems of dyspareunia or changes in sexual desire. In both younger and older patients with sexual problems, questions related to vulvovaginal lesions, discharge, pain, or itching are pertinent.

Finally, the interview includes history of Pap smears including dates and results. Documentation in the chart includes results of the patient's last Pap smear, when and where it was performed, HPV status, and whether there have been any abnormalities in her cytology in the past.

- As this is the most important screening tool that gynecologists have for cervical cancer, it is necessary to collect enough information so the guidelines can be followed and patients can be screened correctly, avoiding unnecessary testing.

2.2 Obstetrical History

Obstetrical history should include number of total pregnancies and the outcomes of each pregnancy, including full term, preterm, abortions (medical or surgical), miscarriages, and number of live children. For reproductive-aged patients, details pertaining the types of delivery, complications such as preeclampsia, and desire for future fertility are documented. This information provides the clinician with the tools necessary to counsel the patient about the risks of future pregnancies or the need for cesarean section. For example, women with previous ectopic pregnancy have a higher probability of having another ectopic pregnancy in the future.

2.3 Medical and Surgical History

Existent medical conditions are basic components of a complete patient interview. In gynecology, it is primordial to know about history of coagulopathies; history of easy bruising; epistaxis, which can explain irregularities in the menstrual period; endocrine or developmental disorders, which can explain problems like infertility; hirsutism; as well as history of malignancies, which can show genetic predisposition to gynecologic cancers. It is also important to review the medical problems of each patient, the medications they are on, and their compliance with medical care:

- Treatment for some conditions can cause gynecologic symptoms or problems in women. An example of this is tamoxifen, an estrogen receptor antagonist used to treat breast cancer, which can cause thickening of the endometrium.
- Patients should be asked about recent weight gain, weight loss, or any other symptoms of thyroid dysfunction. Inquiry should be also made for any signs/symptoms of anemia.

History of previous surgeries will clue the practitioner into the source of a woman's pain, helping to either rule out causes in which organs have been surgically removed, or attribute the pain to the fact that the patient has had previous abdominal surgeries. The location of previous surgery, type (laparoscopic vs open), and procedures performed will give the surgeon the necessary tools needed in case new surgical intervention is needed. This information will also tailor the physical examination to specific parts that are relevant to the individual being seen.

2.4 Family History

Many gynecologic conditions have genetic components that predispose patients to serious diseases, particularly as they become older. Thus, it is important to obtain a detailed family history of first-degree relatives:

- It is known that women with Lynch syndrome have an increased risk of developing endometrial cancer. This is why gynecologists need to inquire about family history of breast, colon, and endometrial cancer.
- Ovarian and breast cancer may have genetic component [BRCA mutations].
- Clotting problems, diabetes, osteoporosis, and dementia can also have a genetic or familial component.

2.5 Social History

Gynecologists are the main care providers for many women. Important questions pertaining to social behavior include amount of alcohol consumed, (how many drinks per week and specific type of drink as alcohol content and effects change), cigarettes smoking (pack per year history and desire to quit), as well as any other drug use:

- If the patient admits to alcohol use, a CAGE questionnaire can be used to determine if the patient is alcohol-dependent or addicted so that the right referrals can be made. This can also lead to the discovery that the patient has an underlying psychiatric disorder, such as depression, that she is self-treating with alcohol.

  The use of drugs such as marijuana, cocaine, crack, and methamphetamines can have serious consequences in the overall well-being of an individual. As physicians, gynecologists have the obligation to offer addiction counseling to all patients who are dependent on any substance. This can improve their overall health status as well as avoid future medical emergencies.

  Tobacco use should be addressed with every patient. If there is a desire to quit, women can be referred to a quit-line and/or given prescriptions such as nicotine patches or gum, as well as antidepressants to aid in this difficult process.
- Patients need to be counseled about the fact that smoking is proven to increase the risk of lung, throat, bladder, colon, rectum, blood, mouth, stomach, esophagus, kidney, and cervix cancer as well as preterm labor, low birthweight, or birth defects.

  Social history also includes domestic violence screening. Specific questions are important to obtain accurate information and make the appropriate referrals. The well-being of the individual in all aspects is the ultimate goal of the health-provider-patient relationship.

3 Focused History/Common GYN Complaints

3.1 Abnormal Uterine Bleeding

- For reproductive-aged women, uterine bleeding becomes abnormal when it differs from a woman's usual cycle. Heavy menstrual bleeding is defined as >80 mL blood loss per period, changing a pad or tampon after less than 2 h, passing clots the size of a quarter or larger, or periods lasting longer than 7 days. It is important to ask how many pads are used during the day with a period and the duration of the period every month (American College of Obstetricians and Gynecologists 2012). In the adolescent female, abnormal bleeding is most likely secondary to immaturity of the hypothalamic-pituitary axis. However, it can also indicate an underlying bleeding disorder (Mullins et al. 2015). In reproductive-aged women, the algorithm of PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) is used to determine the etiology for abnormal uterine bleeding. The most common causes of

bleeding in perimenopausal women include uterine pathologies and anovulatory bleeding.

Postmenopausal bleeding should raise concern for endometrial carcinoma until proven otherwise (Moodley and Roberts 2004). Menopause is defined as 12 months of amenorrhea after the last period. Any bleeding after this should be evaluated immediately. This complaint accounts for about 5 % of office gynecologic visits.

- A common cause of postmenopausal bleeding is vaginal atrophy. Other etiologies include hyperplasia, polyps, and fibroids as well as liver, thyroid, or kidney disease.

3.2 Vaginal Discharge/Itching

Vaginal discharge can be physiologic and found in every woman during the physical exam. However, vaginal discharge is one of the most common complaints that brings patients to the gynecologist's office. Physiologic discharge is clear, cloudy, white or light yellow. Generally, it is scant, watery or very thin, asymptomatic and not foul smelling. Abnormal discharge may represent vaginitis or a sexually transmitted diseases. During the interview, the patient is asked about the onset, duration, consistency, color, odor, and volume of discharge along with sexual history. A complete picture is obtained once a pelvic examination is performed.

3.3 Pelvic Pain

Pelvic pain is a vague and common complaint. Because there can be multiple causes, important questions need to be asked at the time of interview to guide the physical exam. The gynecologist needs to know about the type of pain; exact location and radiation; timing, including if pain occurs during periods or becomes worse during periods; and severity. The effect of associated factors such as sexual activity, menstruation, or physical activity may provide clues as to the etiology of pelvic pain (Reiter 1990). Associated urinary or gastrointestinal symptoms may guide the diagnosis away from a gynecologic cause and referral for further evaluation by other specialists:

- Differential diagnosis for pelvic pain includes ovarian cyst, hemorrhagic cysts, ovarian torsion, endometriosis, adhesions, complication of pregnancy, or pelvic inflammatory disease.
- A comprehensive interview guides the physician to evaluate particular aspects of the physical exam and to which diagnostic studies needed.

3.4 Contraceptive Counseling

Even though there are multiple methods of contraception, not all of them are right for the same patient. It is important at the time of the interview to assess if the patient is using or wants to use contraception for protection against unintended pregnancy or against sexually transmitted diseases or both (Steiner 1999). The patient at this time of the interview needs to talk about prior contraceptive use, as well as medical conditions or social habits that will prevent her from using certain contraceptive methods:

- Both the WHO and CDC have published eligibility criteria for the use of hormones for contraception, including relative and absolute contraindications for their use (US Selected Practice Recommendations for Contraceptive Use 2013; WHO 2012; Centers for Disease Control and Prevention 2010). Migraine headaches, smoking, and hypertension are common problems that limit the use of combination oral contraceptive pills.
- Hormonal contraception such as the birth control pills or progestin IUD or injections can also be used to treat conditions such as menorrhagia secondary to anovulatory bleeding.
- The presence of acne or PMS is often improved on selected combination oral contraceptive pills.

3.5 Infertility

Not being able to conceive is a common gynecologic complaint. Most women think that getting pregnant is easy and that after trying for 1 month they should be able to get pregnant. Thus, it is primordial that patients are explained during their gynecologic visit that infertility is defined as failure to conceive after 12 months of regular intercourse (for 6 months if over 35 years of age). For women with regular cycles, an infertility work-up is generally initiated after 12 months of trying to conceive (Practice Committee of American Society for Reproductive Medicine 2012):

- The gynecologist should inquire about the partner, if he has had any children in the past and if he has had his semen tested to rule out male infertility.
- The initial work-up includes a day 21 progesterone, TSH, metabolic panel, CBC, and blood type and a day 3 FSH for women 35 and older. A pelvic ultrasound or hysterosalpingogram is used to assess tubal and uterine problems.
- Ovulation induction with Clomid or letrozole is used for anovulatory patients.

3.6 Pelvic Organ Prolapse

Pelvic organ prolapse is diagnosed primarily during the physical exam. However, the patient may present complaining of urinary incontinence, looseness on intercourse, splinting, frequent urinary tract infections, vaginal pressure, or a vaginal "bulge."

4 Physical Examination

4.1 When to Start?

ACOG recommends that the initial reproductive health visit should begin between the ages of 13 and 15 (Committee opinion 598 2014) . This should include a complete history, as well as a physical examination including a general examination, visual examination of the breasts, and an external vaginal exam. Pelvic examination is only performed when the patient has a particular symptom or when screening with a Pap smear. An internal examination should be performed if the clinician is concerned about information elicited in the history of the patient Committee on Gynecologic Practice (2012):

- Screening with Pap smear begins at 21 years of age and from then on following ASCCP guidelines. Some practices require that throughout the physical examination, a chaperone must be in the room.

4.2 Components of the Physical Exam

4.2.1 Breast Exam

The breast examination is performed visually first, noting any gross abnormalities, masses, or defects. Palpation is then performed with the preferred technique examining the breast in vertical strips beginning in the axilla and extending in a straight line down the midaxillary line to the bra line. The fingers are then moved medially and continued in an up and down movement between the clavicle and the bra line making circular motions with the pads of the middle three fingers. Each breast area is examined with three different pressures lasting for at least 3 min in each breast (Barton et al. 1999).

4.2.2 Abdominal Exam

Abdominal exam should include inspection, auscultation, palpation, and percussion. The patient is placed in a supine position with legs straightforward or flexed at the knees to avoid contraction of the abdominal muscles. The patient is then told to relax, and the examiner auscultates in the four quadrants listening for bowel sounds. He/she will then proceed to palpate, feeling for masses or tenderness to superficial and deep palpation. Lastly, the abdomen is percussed [tapping on the surface to determine the underlying structure]. A dull sound suggests the presence of a solid mass while a more resonant sound indicates a hollow, air-containing structure.

4.2.3 Pelvic Exam: Bimanual and Speculum Examination

Pelvic examination begins with inspection of the external genitalia. For the first exam, the examiner should have explained to the patient the nature of the examination and the steps entailed. The patient should be comfortable with the examiner. Inspection will allow the practitioner to suspect developmental anomalies (hair distribution, clitoromegaly), vulvar dysplasia or HPV changes (discoloration, redness, growths), or infection (redness, discharge). The Bartholin's glands cannot be palpated when they are healthy:

- The examiner needs to look carefully at the introitus, labia minora, labia majora, clitoris, and perineal body.

Once the external genitalia have been inspected, a speculum examination is used to evaluate the vaginal canal and the cervix. It is important to notice vaginal lesions, signs of atrophy, presence of any growths, or gross lesions. Attention is now turned to the cervix, which is then inspected for lesions, bleeding, or abnormal discharge.

- Cultures should be collected at this point if infection is suspected.
- Cytology is done at the time of the speculum examination.

Bimanual examination can be performed at any point of the exam. It consists of inserting the index and middle finger of the dominant hand of the examiner into the vagina while the other hand is placed on the abdomen. The abdominal hand is then used to push downward while the pelvic hand is used to elevate the uterus and adnexa. Between the two hands, the pelvic organs are evaluated while, at the same time, palpating for masses, cervical or fundal tenderness, and adnexal masses or tenderness. At this point, orientation of the uterus should also be noted.

5 Tests Performed on Exam

5.1 Pap Smear

As previously mentioned, cervical cancer screening starts at 21 years old and after that following ASCCP guidelines depending on results. There are also ACOG and US Preventive Task Force guidelines that are similar. Cervical cancer screening guidelines for average-risk women is shown below:

- HPV testing is generally not recommended in women aged < 30 years but Pap testing is done every 3 years.
- For women over 30, co-testing with cytology and HPV is recommended every 5 years.
- Aged >65 with no low risk for cervical cancer and adequate screening history may stop screening.

5.2 STD Testing

STD testing should be performed when there is high suspicion for a sexually transmitted infection based on history (multiple sexual partners, unprotected intercourse) and examination (abnormal discharge, pelvic pain) or when the patient requests it. STDs such as HIV, syphilis, and hepatitis B and C can be tested in the blood. Chlamydia and gonorrhea are most easily tested in the urine and in a vaginal culture:

- CDC recommended all adults and adolescents from ages 13 to 64 be tested at least once for HIV.
- CDC also recommends that sexually active women <25 years of age or older women with risk factors such as new or multiple sex partner or sex partner with STI to have annual gonorrhea and chlamydia screening.
- CDC recommends syphilis, HIV, hepatitis B, and chlamydia screening for all pregnant women and gonorrhea screening for at-risk pregnant women with repeat testing as needed.

6 Conclusion

The gynecologic history and examination should be a comprehensive review of the patient's health status, which will allow the physician to become familiar with the patient, her comorbidities, and medical needs. Gynecologists are primary healthcare providers, and as such they are responsible for the general well-being of the patient. A comprehensive physical examination will guide the physical examination, diagnostic tests that are needed, as well as treatment. **It is important to establish a good relationship with the patient, as she needs to be open with the healthcare provider and provide all the necessary information.**

Gynecologists are also surgeons, and surgical decisions are made daily based on patient complaints and physical examination. After a complete evaluation of patient symptoms, it is important to perform a complete examination, with appropriate documentation of findings, concerns, and decisions made during the pelvic exam. The complaints and examination findings guide the type of surgery performed and mode of entry. These decisions make a difference in prognosis, recovery time, and overall return to a regular, healthy lifestyle. Limitations should be recognized, and appropriate referrals should be made to different specialists when other findings are encountered in the physical examination. Every year, women after age 30 should be evaluated for screening mammography, women over 50 should have a colonoscopy, and women over 65 [or earlier based on risk factors] should have a DEXA scan.

> As primary care providers, gynecologists are responsible to make the appropriate health and lifestyle arrangements for their patients.

An appropriate, complete, and accurate history and physical examination help to assure that all the patient's issues, concerns, and risk factors are addressed. A solid, high priority, and trusting relationship with their gynecologist can lead our patients to a healthier and happier life.

7 Cross-References

- ▶ Basic Management of Infertility
- ▶ Breast Cancer Screening
- ▶ Contraception and Family Planning
- ▶ Management of Abnormal Uterine Bleeding – Later Reproductive Years
- ▶ Management of Cervical Dysplasia
- ▶ Management of Intraepithelial Lesions of the Cervix
- ▶ Management of Menopausal Symptoms
- ▶ Management of Risks Factors for Older Women: Osteoporosis and Cardiovascular Disease
- ▶ Management of Uterine Fibroids
- ▶ Management of Vulvodynia
- ▶ Work-Up and Management of Polycystic Ovarian Syndrome

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Contraception and Family Planning

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Contents

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Abstract

Family planning is a critical issue in the field of women's health. Both hormonal and non-hormonal forms of contraception are available to women. A woman's long-term goals, personal beliefs, and medical conditions impact heavily on her choice of contraception. While many of these methods are encouraged to be used prior to unintended pregnancy, this chapter will also address emergency contraception, as well as methods for pregnancy termination. The US Medical Eligibility Criteria for Contraceptive Use, developed by WHO and modified by the US CDC, comprises guidance recommendations for the use of specific contraceptive methods by women and men who have certain medical conditions or characteristics.

Keywords

Sterilization • Contraception • Abortion • Emergency contraception • Postpartum insertion • Tubal ligation • Oral contraceptive pills • Contraceptive implant • IUD • Barrier methods • Unintended pregnancy • Hysteroscopic sterilization • Levonorgestrel IUD • Copper IUD • Progestin-only pills

1 Introduction

Almost half of pregnancies in American women are unintended, and four in ten of these unintended pregnancies are terminated by abortion. At least half of American women will experience an unintended pregnancy by age 45 (Guttmacher Institute). Unintended pregnancy is a major public health issue given that these pregnancies are at higher risk of poor maternal and fetal outcomes. Therefore, addressing family planning is an imperative part of the provision of comprehensive reproductive health care.

When counseling a woman on her options for contraception, there are several factors that should be taken into consideration including her reproductive life plan, her medical history, and her personal preference regarding contraception options. This chapter will discuss the diverse options of birth control now available to women at multiple stages of their life, including the peripartum period. The US Medical Eligibility Criteria for Contraceptive Use is available online to provide recommendations for women with certain medical conditions or characteristics (CDC 2010).

2 Contraceptive Efficacy

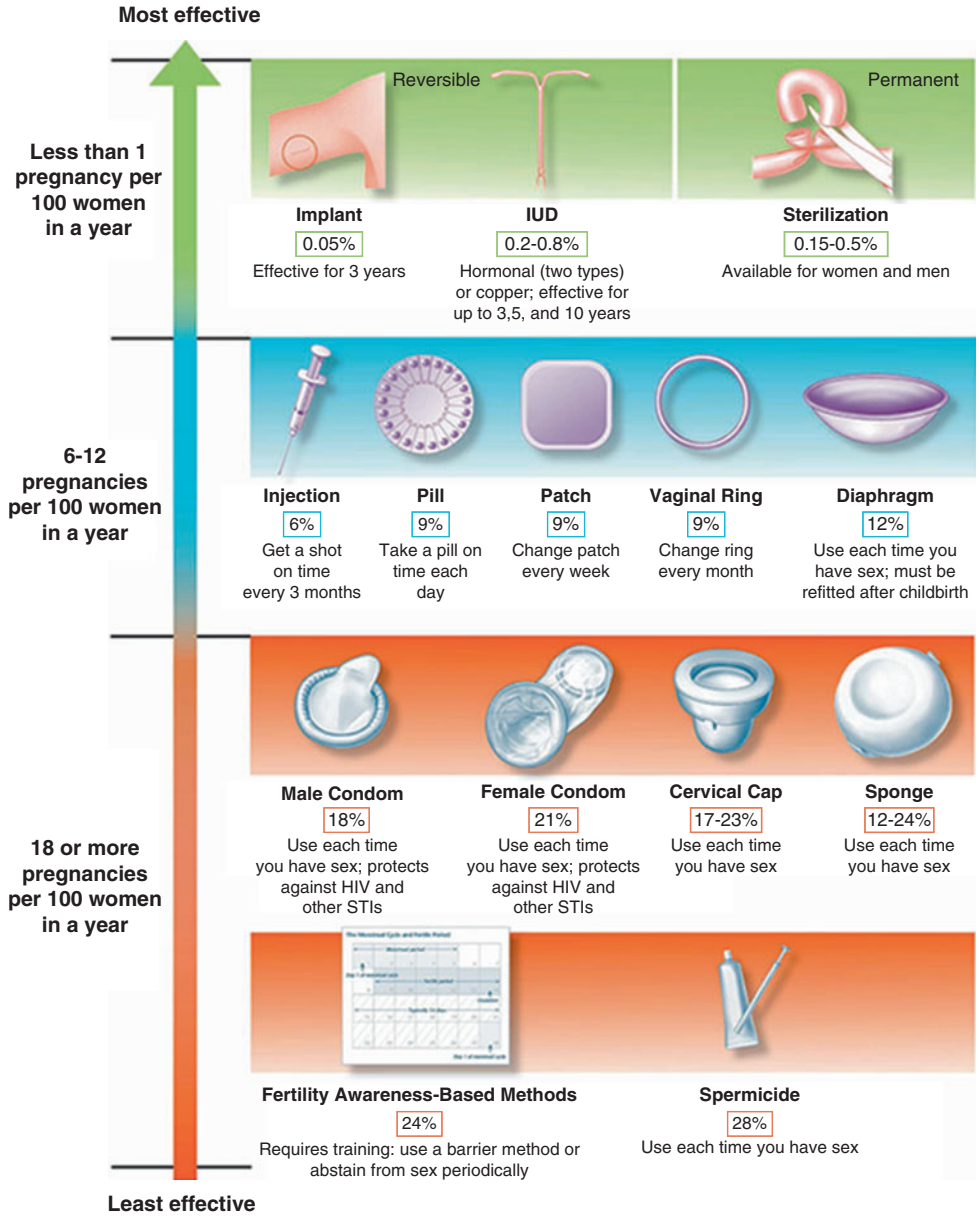
Contraception options are often discussed based on their efficacy in pregnancy prevention. The WHO and CDC have organized the contraceptive methods into "tiers of effectiveness" based on their failure rates. Methods within the first "tier" include both reversible and irreversible methods, such as the IUD, implant, male sterilization, and surgical female tubal occlusion. Tier 1 methods have a failure rate of <1% per year. Methods within the "second" tier include oral hormonal contraceptives, transdermal formulations, and injections. Their failure rate ranges from 6% to 12% per year. The least effective, or third "tier," includes barrier methods, natural family planning, or withdrawal methods where failure rates are greater than 18% per year (Fig. 1).

While this chapter will review the methods of contraception based on the WHO tier of effectiveness, it is important to individualize counseling that considers each patient's goals and wishes. The ideal method of contraception for a woman is the one that will fit her needs and the one that she will use safely and consistently.

3 Tier 1: Highly Effective Methods of Contraception

3.1 LARC (Long-Acting Reversible Contraception) Methods

Long-acting reversible forms of contraception are highly effective devices that can be easily placed and removed in the outpatient setting. They provide the highest effectiveness rates and a rapid return to fertility after removal. Failure rates of



Other methods of birth control

Lactational amenorrhea method: This is a temporary method of birth control that can be used for the first 6 months after giving birth by woman who are exclusively breastfeeding.
Emergency contraception: Emergency contraceptive pills taken or a copper IUD inserted within 5 days of unprotected sex can reduce the risk of pregnancy.
Withdrawal: The man withdraws his penis from the vagina before ejaculating: 22 out of 100 women using this method will become pregnant in the first year.

Fig. 1 Tiers of effectiveness for birth control methods from ACOG Committee Opinion 642, Oct 2015. Abbreviations: HIV, human immunodeficiency virus; IUD, intrauterine device; STIs, sexually transmitted infections. *Percentage of women who will become pregnant within the first year of typical use of the method

these devices are <1% per year given that they do not rely on the user for their efficacy as they are "forgettable." Unlike most forms of contraception, typical use is comparable to perfect use given that there is little to no impact on the device performance by the user. There are three methods of LARC available in the USA, two of which are intrauterine devices: the copper IUD and levonorgestrel intrauterine systems (four available choices). The third form of LARC method is the etonorgestrel single-rod implant.

Data reported from the Contraceptive CHOICE project, a prospective cohort of women aged 14–45 years, showed that in the absence of barriers (i.e., financial, knowledge, health care provider, or logistical barriers), the rate of initiation of LARC was higher than any other contraceptive method (Secura 2010). According to the American College of Obstetrics and Gynecology (ACOG 2011), best practices for LARC insertion include (1) provision of LARC on the day of request if pregnancy can be excluded; (2) to offer LARC after delivery, abortion, or D + C for miscarriage; (3) screening for STIs at the time of insertion and treatment for positive results with IUD remaining in place; and (4) to offer the copper IUD as the most effective method of emergency contraception.

4 Intrauterine Devices

4.1 Copper IUD

The Copper T380 IUD, also known commercially as the *ParaGard*, is a T-shaped device of polyethylene wrapped with copper wire around the stem and arms. It prevents >99% of pregnancies by several mechanisms, including inhibition of sperm migration and viability, change in transport speed of the ovum, and damage to or destruction of the ovum by creating a sterile inflammatory response in the uterus. All effects occur preimplantation. It is FDA approved for 10 years of use and is a good option for women who have concerns about hormonal effects. The most common reported side effect is longer and heavier bleeding and pain with menses. Although all women should be counseled regarding this, women with dysmenorrhea or problems with heavy bleeding need particularly careful consultation.

- The copper IUD has a reported failure rate at 1 year of 0.8 per 100 women and a 10-year failure rate comparable with that of female sterilization (1.9 per 100 women over 10 years). An additional benefit to the copper IUD is that it can be used as emergency contraception up to 5 days after unprotected sexual intercourse and is >99% effective as emergency contraception.

4.2 Hormonal IUD

The levonorgestrel intrauterine system (LNG-IUS) currently comes in four forms: commercially known as the *Mirena*, *Skyla*, *Kyleena*, and *Liletta*. The levonorgestrel intrauterine system is T shaped with a polydimethylsiloxane sleeve containing levonorgestrel on the stem of the T. This sleeve contains 52 mg of levonorgestrel and it releases 20 microgram/day (down to 10 mcg/day after 5 years). The Mirena is FDA approved for 5 years. The Skyla initially releases 14 mcg/day of levonorgestrel, is FDA approved for 3 years, and is marketed toward younger, nulliparous women for its smaller size and reportedly easier insertion. The Liletta has the exact same components and size as Mirena, but it has a different inserter and lower cost. It is currently FDA approved for only 3 years. The recently introduced Kyleena is the same size as the Skyla, is approved for 5 years of use, and initially releases 17.5 mcg/day [an average 9 mcg/day over 5 years].

- The primary mechanism of action is to prevent fertilization. The local action of progestin causes the cervical mucus to become thick and impenetrable by the sperm. Like the copper IUD, the LNG-IUS also creates a hostile environment for sperm motility in the uterus and does not have any effect postimplantation. The small amount of steroid additionally causes endometrial suppression. The endometrial suppression results in lighter menses as

well as amenorrhea in 20% of users. The reduction in menses [after 2–3 months of insertion] is a characteristic that many women desire.
- Mirena reduces heavy periods by 90% in 6 months. Mirena is the first and only birth control that is FDA approved to treat heavy periods (>80 ml in cycle, i.e., soak through a pad or tampon in 2–3 h) in women who choose intrauterine birth control.
- Very little hormone is absorbed systemically although a small number of women may experience hormone-related side effects, particularly the first year of use.

Contraindications to IUD placement include pregnancy, untreated acute cervicitis, known active pelvic infection, concerns for uterine malignancy, breast cancer, acute liver disease, or uterine anomaly. If there is an active pelvic infection present, the woman should be treated appropriately prior to placement. One common myth is that women with a history of PID or history of STIs are not candidates for IUD. A gonorrhea/chlamydia test can be obtained at the time of placement, and placement does not need to be deferred until after results return unless there is a suspicion for active infection. If positive STD screening is discovered after the IUD insertion, the patient can be appropriately treated with the IUD still in place.

A woman with a positive pregnancy test and an IUD has an increased risk of ectopic pregnancy compared to a woman without an IUD. However due to the IUD's extremely effective ability to prevent any pregnancy, her overall risk of ever getting an ectopic pregnancy is lower than other sexually active women not using contraception. History of ectopic pregnancy is not a contraindication to IUD placement. Anatomical distortion of uterus should be handled on a case-by-case basis between the woman and her provider. IUDs can be safely used in adolescent women and in women who are nulliparous.

Although pain on insertion of the IUD is much less in women after at least one pregnancy, the benefits generally make the method desirable for all age groups. The use of vaginal or buccal Cytotec pills and/or NSAIDs prior to insertion is commonly used to decrease pain. The use of a paracervical block or oral Ativan pretreatment is less common.

5 Progestin Implants

The progestin-only implant is a LARC method that is FDA approved for 3 years and is placed in the outpatient setting. Available as the *Nexplanon* in the USA, it is a single rod inserted subdermally in the inner upper arm with local anesthesia. It consists of an ethylene vinyl acetate copolymer core containing 68 mg of etonogestrel. The primary method of action of the implant is suppression of ovulation. Additionally, it thickens cervical mucus and alters the endometrial lining. After proper placement, the implant is easily palpated and can be removed by a small incision in the skin near the tip of the implant. In rare cases where the implant may have migrated, Nexplanon can be located with x-ray, MRI, or ultrasound imaging. Pregnancy rate with the contraceptive implant is the lowest of any method at 0.05%.

For most women bleeding is altered significantly after insertion but is often decreased. Side effects typically include amenorrhea, irregular or prolonged bleeding, and progestin-related side effects. Insertion complications are 1.0% and include pain, hematoma formation, and unrecognized noninsertion (it is very important to check palpation of the implant after insertion). Removal may be complicated by breakage of the implant or inability to palpate the implant due to deep insertion. The implant should only be placed by a provider who has completed the training from the manufacturer.

6 Permanent Contraception: Sterilization

6.1 Male Sterilization

Vasectomy is a surgical procedure involving interruption of the vas deferens. It is commonly performed in the outpatient setting, making it in

comparison more cost-effective, safer, and a shorter procedure than female sterilization. Many are performed using a no-scalpel technique. Complications include bleeding, infection, and chronic testicular pain, but these are rare. The patient needs to confirm azoospermia with his provider approximately 3 months after the procedure (Bartz 2008). A backup form of contraception must be used during this time. Vasectomy should be considered a permanent procedure although it is reversible in some cases. Success of pregnancy following reversal is dependent on the type of procedure, the time since the procedure, and the age of the patient.

6.2 Female Sterilization

Female sterilization is second only to oral contraceptive pills as the most common method of contraception used among reproductive age women in the USA. Surgical methods involve permanent occlusion of the fallopian tubes either through open or laparoscopic transabdominal procedures or via a transcervical approach using hysteroscopy. Typically in the postpartum period, a partial salpingectomy, modified Pomeroy, or Parkland method is performed. Occlusion of the fallopian tubes can also be done with laparoscopic application of Filshie clips, Hulka clips, or Falope rings. Higher failure rates can occur if the devices are incorrectly placed, the applicator is not calibrated, or if proper application is limited due to an enlarged fallopian tube. Cauterization of the tubes using bipolar cautery can also be done through laparoscopic approaches. The efficacies of the methods are shown to have an overall pregnancy rate that ranges from 0.5% yearly (WHO, CDC 2010) to 18.5/1000 women/year (Peterson et al. 1996).

Hysteroscopic tubal sterilization can be performed in the office setting with local anesthetics and NSAIDs. A woman's coexisting medical problems such as obesity and cardiac or pulmonary disease may make this less-invasive approach safer. The *Essure* is a steel and nickel coil inserted transcervically through hysteroscopy into the fallopian tubes. Over a period of months, an inflammatory reaction causes tubal occlusion. Given this time period, a backup form of contraception must be used until bilateral tubal occlusion can be confirmed by hysterosalpingogram after 3 months. This approach has an efficacy similar to other methods of tubal occlusion and allows for faster recovery. Intrauterine fibroids, congenital anomalies, or scarring may limit the use of this device.

When counseling a woman who is considering permanent contraception, it is important to discuss her medical health, her tolerance to office procedures, the safety of abdominal surgery and general anesthesia, and her compliance with follow-up testing if needed. It is recommended that during the counseling, the provider offers LARC methods as an alternative since they are as effective as surgical options and they are easily reversible. It is important to counsel women that permanent contraception is irreversible although some methods can be reversed with success rates relating to type of procedure, age of the patient, and years since the ligation procedure.

7 Tier 2: Moderately Effective Forms of Contraception

7.1 Hormonal Contraception

Options for hormonal contraception included combined hormonal contraceptives (CHCs) and progestin-only methods.

7.1.1 Combined Hormonal Contraceptives (CHCs)

Combined hormonal contraceptives contain ethinyl estrogen or estradiol valerate and a formulation of a progestin. They act by suppressing ovulation through inhibition of GnRH, thus preventing the LH surge. CHCs also thicken cervical mucus and create an inhospitable environment in the uterus for implantation, although these play a minor role. Many women use CHCs for conditions beyond preventing pregnancy including dysmenorrhea, PMS, hirsutism, acne, and irregular, heavy, or unpredictable cycles. Combined hormonal contraception has also been shown to

decrease the risk of endometrial cancer (Mueck et al. 2010) by approximately 50%, as well as an approximately 50% decrease in ovarian cancer when used for over 10 years (Havrilesky et al. 2013).

Side effects of combined oral contraceptives include nausea, mastalgia, headaches, and decreased libido. New lower dose CHCs tend to reduce these side effects. These side effects, however, are highly patient dependent and difficult to predict. If a woman complains of side effects that are intolerable after a 2–3-month period of use, she can be switched to a different formulation with often good results.

- It is important to note that CHC is contraindicated in women at high risk for thromboembolic events including women with a history of cigarette smoking over the age of 35, hypertension, migraines in women over the age of 35, migraines with aura in any woman, antiphospholipid antibodies, or history of hematologic disorders with risk of clot. Current or past history of breast cancer is also relative/absolute contraindication for combined formulations. A detailed history excluding any possible contraindications should be obtained by the provider prior to prescribing.

The pill is taken daily and should only be used by women who feel this is doable for them. Most pill formulations contain a 4–7-day window that is hormone-free, during which the woman will have her menses. Monophasic pills have the same amount of hormone per each active pill and can be taken continuously to avoid menses although break through bleeding may occur. A backup method of contraception should be used in the first 7 days of initiating combined hormonal contraceptive pills. It is important that women should be counseled that daily use of the pill is mandatory for prevention against pregnancy. If a woman misses a single dose, she should take the missed dose as well as soon as possible. If she misses more than one dose, she should use a backup method through her next menses. Without this precaution, she should use a form of emergency contraception, as she is at risk for an unintended pregnancy. The more recently introduced 4-day window pills are designed to create lighter periods.

Combined hormonal contraceptives also come in a transdermal formulation, containing ethinyl estradiol and norgestimate. "The patch" is applied weekly for 3 weeks, with then skipping 1 week in order to induce menses. Women who enjoy the benefits of combined hormonal formulations, but do not want to remember taking a daily pill, may prefer this route of administration. It is comparable in efficacy to combined oral formulations and works in a similar mechanism of action (Hedon et al. 2000). It is unclear whether the transdermal formulation puts women at an increased risk of thromboembolic events compared to current oral formulations (Jick et al. 2010). The transdermal patch provides a steady state of hormones, unlike the pill which provides peak and trough levels. If the user forgets to change the patch, there is a 48-h window of continued hormonal protection. Beyond this time, the woman is cautioned to use another form of contraception or to use emergency contraception if unprotected intercourse has occurred.

The ring, branded as NuvaRing, is a combined hormonal contraceptive that consists of ethinyl estradiol and etonogestrel. It is placed vaginally for a total of 3 weeks and then removed for 1 week to induce menses. It may be used continuously for 4 weeks and then replaced in women who desire amenorrhea. Unlike the patch, it is not visible to others and does not normally pose a problem during sexual intercourse. Vaginal irritation or discharge is a common side effect.

7.1.2 Progestin-Only Oral Formulations

A large proportion of the contraindications (see above) of oral combined formulations can be avoided by using progestin-only oral formulations. Good candidates include breastfeeding women, hypertensive women, and women over 35 that smoke, have migraines, or have risk factors for clotting problems. The mechanism of action involves thickening of the cervical mucus making it difficult for sperm to pass, blocking

ovulation in 40% of women, and thinning of the endometrium to resist implantation. The pill must be taken at the same time every day. This is especially true with Micronor, available in the USA. A backup form of contraception should be used for 2 days [like a condom] if the woman delays the next pill by more than 3 h.

The most common side effect is irregular spotting, which may be unacceptable to some women. A thorough history and physical examination should be performed before prescribing these medications to identify any contraindications, although relative and absolute contraindications to the progestin pill are rare but include malabsorptive procedures, positive for antiphospholipid antibodies, current or past breast cancer, liver cancer, certain anticonvulsants [okay for lamotrigine], and severe decompensated cirrhosis.

7.1.3 Depot Medroxyprogesterone Acetate (DMPA)

DMPA is an injectable form of contraception which consists of only progestin, as its name suggests. It is effective for 3 months and is available as an intramuscular (IM) and subcutaneous (SC) injection. The IM dose cannot be given at home and thus, users will need to see a provider each time. Its mechanism of action is similar to the oral formulations described above although suppression of ovulation is around 100%. The hormonal effects slowly increase initially and then taper off, resulting in the need for another injection after 3 months.

If used properly DMPA is comparable in efficacy to intrauterine devices, but its effectiveness is often limited by users needing to return for repeat injections. A backup form of contraception must be used for approximately 7 days if the injection is not given during first 5 days of a normal menstrual cycle. Side effects include irregular bleeding, particularly the first 3 months of use, but many women become amenorrheic within the first year. A small percentage of women gain weight on this method; thus if significant weight gain occurs, it is important to address this with the patient. Women should be carefully counseled that unlike other forms of contraception, there can be a delay to returned fertility of up to 18 months (Schwallie and Assenzo 1974).

Many providers will defer on DMPA as a contraceptive choice due to concern of its effects on bone mineral density. The FDA, in 2004, placed a "black box" warning on DMPA cautioning the use of DMPA beyond 2 years if no other adequate forms of contraception are available. However, ACOG and WHO have recommended that there should be no limitation of the length of time DMPA is used and that there is no indication for bone mineral density testing in the low-risk women as numerous studies have shown that bone density resolves after discontinuation of DMPA and changes are not permanent (Lopez et al. 2014; Harel et al. 2010).

- Other benefits of DMPA include decreased risk of endometrial cancer, iron deficiency anemia, pelvic inflammatory disease, ectopic pregnancy, symptoms of endometriosis, dysmenorrhea, sickle cell crisis, and seizures.
- The contraindications include multiple risk factors for arterial cardiovascular disease, current DVT or PE, active liver disease, history of breast cancer, vascular disease, and history of stroke or diabetes for 20 years.

8 Tier 3: Less Effective Forms of Contraception

8.1 Natural Family Planning Methods

Many patients will often ask providers for information regarding natural family planning. Despite their high failure rates, they remain an option for women who understand these risks and desire a nonhormonal, nonsurgical, non-barrier method. These methods, however, are highly dependent on a woman having regular, predictable cycles so that she can estimate the time of ovulation. In addition, her and her partner must be willing to abstain from sexual intercourse around ovulation. Family planning methods include those based on the timing of her cycles (calendar method),

symptothermal methods, and the ovulation method.

- With the calendar method, a woman must have regular menstrual cycles, every 26–32 days, and be aware of the exact timing of her cycles. This can be achieved by tracking her periods for ≥6 months. The calendar method is not appropriate for women who are breastfeeding, have irregular cycles, or are unable to time their cycles. The goal is to abstain from sexual intercourse during the fertile period, approximately days 8–19 of her menstrual cycle (Arévalo et al. 1999).
- The symptothermal method is based on the rise in body temperature which occurs following ovulation. This rise is often less than a degree of Fahrenheit and must be taken immediately upon rising at the same time daily. Sexual intercourse is avoided from the start of menses until after 3 days of the spike in body temperature, indicating to the woman that ovulation has occurred.
- The symptothermal method can be used in conjunction or separately from the evaluation of cervical mucus as well. Transparent secretions often indicate the beginning of the fertile cycle, while thick, sticky secretions often indicate the less fertile period. These findings are charted by the woman in conjunction with her body temperature, delineating a short time period each month where she is less likely to become pregnant. Many sample charts are available online for women to use, and the provider should encourage reviewing the validity of the chart, as well as to encourage proper use.

8.2 Lactational Amenorrhea Method (LAM)

Lactational amenorrhea is the temporary postnatal infertility that occurs when a woman is amenorrheic and fully breastfeeding (Trussell 2011). Studies have reported that women that are exclusively breastfeeding around the clock and who have amenorrhea are very unlikely to get pregnant. Women are often cautioned to avoid sexual intercourse in the first 6 weeks following birth, to facilitate healing and prevent the risks of early pregnancy. It is not uncommon, however, for women to have intercourse within a month after delivery. Many women are hesitant to use birth control in this period and will be interested in lactational methods. The induction of prolactin from breastfeeding dampers the pulsatile action of GnRH, thus preventing an LH surge and subsequent ovulation.

- The lactational amenorrhea method is only effective when the following strict conditions are met: the woman is exclusively breastfeeding (or breast pumping) every 3–4 h (including during the night); the infant is less than 6 months old; the infant is receiving minimal, if any, supplemental nutrition; and the woman has not yet menstruated.

8.3 Withdrawal and Spermicides

Withdrawal involves removal of the penis from the vagina during sexual intercourse prior to ejaculation. Unfortunately, the pre-ejaculatory fluid can often contain sperm, with one study demonstrating 37% of male participants with motile sperm in the pre-ejaculatory fluid (Killick et al. 2011). Withdrawal is thus not an effective form of birth control and should not be recommended as such.

Most spermicides contain an active ingredient called nonoxynol-9, which damages the cellular membrane of sperm, rendering them ineffective in fertilization. Spermicides are available in foam, gel, cream, and suppository method and are often used in conjunction with barrier methods or withdrawal.

- Spermicides have a high failure rate of often over 20% and also do not provide protection against sexually transmitted diseases when used without barrier methods.

8.4 Barrier Methods

8.4.1 Male Condom

Male condoms are one of the most common forms of contraception. They are an effective form of protection against sexually transmitted infections (STIs) when made from latex. Most condoms are made from latex, but materials such as lambskin are also used, and they do not infer the same protection against STIs. Male condoms can be used in conjunction with spermicides. Condoms must be used with each encounter of sexual intercourse to be effective, cover the entire penis, and be discarded immediately after each use.

- Given that latex condoms can provide limited protection against STIs, condoms can be used in conjunction with more effective forms of contraception. They are readily available, even in resource-poor settings, relatively low cost, and easily disposable.
- Typical use of condoms results in approximately 18 out of 100 women becoming pregnant after 1 year.

8.4.2 Female Methods

The female condom (femidom) is similar to the male condom in that it is a sheath which should provide a barrier method between the penis and the vagina. While a less-used form of contraception today, it is important for providers to be aware of its proper use. A female condom consists of a sheath with a ring at each end, one closed to cover the cervix and one open for the introitus. The first-generation female condoms used polyurethane sheaths. The newer-generation condoms use nitrile in order to lower cost and reduce the crinkling noises or a polyethylene resin designed to be stronger, thinner, and more sensitive. A recent version of the female condom uses natural latex, the same material as in a male condom. New designs of female condoms include sponges that secure the sheath inside a woman's vagina or a polyurethane pouch that is enclosed in a dissolving capsule to aid in insertion. New materials and designs are under clinical trials.

- Typical use shows pregnancy rates to be slightly higher than male condoms, and there is limited data available in regard to the protection against STIs.
- Other disadvantages to the female condom include limited availability compared to male condoms and dependence on proper, blind insertion.

The diaphragm is a cup that is placed inside the vagina, to cup and completely cover the cervix. It must be fitted to the woman and be placed prior to sexual intercourse. As with male condoms, it can be used with water-based spermicides that is placed before intercourse and on the cervical side of the diaphragm. The diaphragm is a reusable form of the female condom. It should be regularly cleaned and inspected for defects. It must remain in the vagina for 6–8 h after a man's last ejaculation. For additional acts of intercourse, it is recommended that 5 ml additional spermicide be inserted into the vagina.

- Latex diaphragms should be replaced every 1–3 years, while silicone diaphragms can last up to 10 years.
- Diaphragms should be removed and cleaned at least every 24 h.

The cervical cap is a silicone cup that inserted into the vagina. Spermicide is placed in the dome of the cap and spread over the brim. The cap is placed over the cervix, making sure that the entire cervix is covered. The cap is left in place for 6 h after intercourse and removed at least every 48 h.

9 Postpartum Contraception

The intrauterine device can be inserted immediately postpartum within 10 min after delivery of the placenta. While the rates of expulsion are higher compared to nonpregnant women, this provides a convenient time for placement, avoiding the return office visit, discomfort from the additional procedure, and is especially useful in low-resource settings. Progestin-only oral,

progestin injectable, and the progestin implant contraceptives are an option for women in the immediate postpartum period as well, with no affect on breastfeeding. Combined hormonal contraception (pill, patch, ring) should be avoided at least for the first 3–4 weeks postpartum as the risk of VTE is high and in all breastfeeding women as it may inhibit milk production. Transabdominal tubal sterilization can easily be performed within 48 h of delivery. The fallopian tubes of the postpartum uterus can often be reached through an umbilical incision.

10 Emergency Contraception

Postcoital contraception, or emergency contraception, is indicated for women who have had unprotected intercourse and wish to avoid pregnancy. This often includes women who are currently using contraception, but may have imperfect use such as missing two or more pills or forgetting to replace a transdermal patch. It also includes having a condom break or slip and in cases of sexual assault. Effective and currently approved formulations for emergency contraception include hormonal regimens and the copper intrauterine device (ACOG 2010). It is important to note that these regimens are not abortive, as they act before a pregnancy has been established. Common side effects include nausea, headache, and irregular spotting or menses for a short period after use.

- Plan B is a one pill option that must be taken within 72 h of unprotected intercourse. It is available over the counter without a prescription or age restrictions.
- Ella contains ulipristal, a drug that blocks ovulation. It is available only with a prescription. It is one pill also that can be taken up to 120 h after sex.
- The copper IUD works by preventing implantation 5–7 days after intercourse.

There are very few contraindications to emergency contraception, and most often the risk of pregnancy outweighs the risk of emergency contraception. There is no indication for pregnancy testing prior to administration, and the oral options are most effective the closer taken to the coital act. Victims of sexual assault should be offered emergency contraception as soon as possible. While there are no contraindications to multiple uses of emergency contraception, it is less effective than consistent forms of contraception. Providers can use these opportunities to offer more consistent and reliable methods of birth control to their patients emphasizing the LARC methods.

10.1 Oral Formulations

There are two types of oral, hormonal emergency contraception in the USA, a progestin-only method and ulipristal acetate.

The most commonly used emergency contraception is levonorgestrel 1.5 mg which can be taken in a single dose. Most providers recommend taking levonorgestrel 1.5 mg as a single dose as opposed to 12 h apart due to reportedly fewer side effects and higher efficacy. It should be taken as soon as possible after unprotected sexual intercourse, but is effective up to 72 h after. Its efficacy decreases over time. The levonorgestrel method for emergency contraception is available over the counter without age restriction.

A second emergency contraceptive method is ulipristal acetate, selected progesterone receptor modulator or antiprogestin that results in a delay in ovulation. A dose of 30 mg can be taken up to 120 h after unprotected sexual intercourse. No clinical exam or pregnancy test is necessary prior to the provision of hormonal emergency contraception, and there are no contraindications to these methods. Ulipristal acetate requires a prescription.

In regard to efficacy for pregnancy prevention, ulipristal acetate is more effective than levonorgestrel up to 5 days after unprotected intercourse, with a lower pregnancy rate of 1.4% compared with 2.2% pregnancy rate with levonorgestrel.

A combined estrogen-progestin regimen using oral contraceptives was used for many years before the currently available options were

available. Use of this regimen has fallen out of favor due to side effects and higher efficacy of the aforementioned dedicated products.

10.2 Intrauterine Devices

The copper IUD can be used as an emergency contraceptive method up to 5 days after unprotected sexual intercourse. It is effective by hindering sperm mobility and function. It is over 99% effective as emergency contraception during the time period. The copper IUD is an effective form of emergency contraception, and after insertion it can then be used for long-term, highly effective, and reversible contraception. The levonorgestrel IUDs are currently being investigated as a form of emergency contraception.

10.3 Contraception in Women with Medical Conditions

One common concern for providers is how to approach the patients with medical conditions that may limit their options for birth control. Resources exist for to assist providers in contraceptive choice. The CDC contraception "app" contains the US Medical Eligibility Criteria for Contraceptive Use (2010). Providers can search either by medical condition or choice of contraception. Each formulation of contraception is categorized from 1 to 4, based on the risk of its use with a particular medical condition (see Table 1).

Table 1 Categories of eligibility criteria for contraceptive use

1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition for which the theoretical or proven risks usually outweigh the advantages of using the method
4	A condition that represents unacceptable health risk if the contraceptive method is used

CDC contraception (2010)

10.4 Termination of Pregnancy

Millions of abortions are performed each year, with a large proportion of these being carried out in nonclinical and hazardous settings. When performed by an experienced provider, however, such as the majority of those in the USA, the procedure is safe, with a morbidity and mortality rate much less than rates associated with childbirth (Raymond and Grimes 2012). A woman's decision to proceed with an abortion is a complex one, and the provider should approach the discussion in a nonjudgmental manner. If the provider does not offer abortion services, they should direct the patient to a provider who can. Post-procedure contraception should be discussed as ovulation can occur soon after termination.

- A thorough history and physical should be performed, paying careful attention to the woman's last menstrual period (LMP) for dating purposes. An intrauterine pregnancy should be confirmed with imaging and confirmatory dating. Rh status, type, and screen and, in some cases, a complete blood count should be obtained.

10.4.1 Medical Abortion

Medical abortions are often performed up in the first trimester, with the majority of these being in the first 63 days of gestation (ACOG 2014). The benefits of medical abortion include avoiding surgery and the risks of anesthesia. Medical abortion requires close follow-up, is completed over a number of days, and will usually result in the passage of products at home. There are multiple regimens known for the purposes of medical abortion in the first trimester using mifepristone, methotrexate, and/or misoprostol (see Table 1). Mifepristone is a progesterone antagonist, which interrupts the products of conception (POC). Misoprostol is a prostaglandin which causes contractions of the uterus to expel the POC. Methotrexate inhibits dihydrofolate reductase, interrupting DNA synthesis. Side effects of these medications include headache, nausea and vomiting, and diarrhea.

- The FDA-approved regimen calls for mifepristone 600 mcg PO followed by misoprostol 400 mcg PO 48 h later. It is approved for use in pregnancies up to 49 days gestation with an overall success rate of 92%.
- The evidence-based regimen calls for mifepristone 200 mg PO followed by misoprostol 800 mcg vaginally, buccally, or sublingually 24–48 h later. Alternatively, misoprostol can be placed less than 6 h after mifepristone if placed vaginally. This regimen can be used up to 63 days gestation with an overall success rate of >95%.
- A third regimen involves misoprostol 800 mcg vaginally or sublingually every 3 h for a total of three doses. This regimen has a higher rate of side effects and a decreased success rate of approximately 85%. Methotrexate is given at 50 mg/m^2 intramuscularly with misoprostol 800 mcg given vaginally 3–7 days after. This regimen is over 92% effective up to 49 days of gestation.

Women should be counseled on the expected amount of bleeding and to seek further care if she is soaking through multiple pads per hour or becomes symptomatic (dizziness, loss of consciousness, etc.). A small proportion of women will require a surgical procedure to evacuate retained products of conception.

- Contraindications to medical abortion include history of coagulopathy, severe anemia, allergies to the medications, or ectopic pregnancy. Providers should use caution in providing medical abortions if the woman is anemic, has a history of noncompliance, or does not have the ability to easily reach an emergency facility.
- Pain is best managed with nonsteroidal anti-inflammatory drugs.

There is currently no data that suggests mandated use of antibiotics in medical abortion. Women should be counseled to see their provider if they develop signs of infection, such as fevers or foul-smelling discharge. Both misoprostol and methotrexate are associated with teratogenicity in the first trimester (including limb defects, craniofacial abnormalities), and patients must be counseled that termination is recommended in a continuing pregnancy.

In the second trimester, labor can be induced with prostaglandins. This method has a higher risk of infection, bleeding, retained products of conception, and other complications compared to a dilation and evacuation, but may be preferable to some women rather than a surgical procedure. It is important to inform women of the risks and benefits of each option. Women should be counseled that curettage or evacuation is a possibility following a failed medical abortion in either the first or second trimester.

10.4.2 Surgical Abortion

Surgical abortion techniques and methods have evolved over time to improve safety and efficacy. In the first trimester, surgical abortion is commonly performed with suction dilation and curettage, either with electric vacuum aspiration (EVA) or manual vacuum aspiration (MVA), and is preferred over sharp curettage to decrease risk of bleeding, infection, perforation, retained products of conception, and uterine trauma. Depending on the patient and provider's comfort level, this procedure can be performed in either the office or hospital setting. In a low-risk woman, anesthesia can be achieved with a local block or intravenous sedation. Depending on the gestational age, the provider may wish to use misoprostol as a cervical ripening agent prior to the procedure (can be given a few hours prior). Pre-procedural dilators are rarely required in the first trimester. In the procedure, the size of the cannula used will often be the approximate gestational age. Electric or manual vacuum aspiration are both highly effective for uterine evacuation.

Antibiotics should be given in the setting of induced abortion. 100 mg PO of doxycycline should be given 1 h prior to and 200 mg PO following the procedure. Complications are very rare, but include uterine perforation, incomplete evacuation of products, infection, and reaction to anesthesia.

Dilation and evacuation is performed in the second trimester. Compared to labor induction termination, dilation and evacuation have decreased risk of bleeding, infection, and retained products of conception; however it requires a skilled provider. Preoperative osmotic dilators can be placed in the cervix the day prior to the procedure and include polyacrylonitrile (Dilapan-S) or *Laminaria japonica*. The dilators absorb moisture, causing softening and dilation of the cervix. On the day of the procedure, the cervical dilators are removed, and then the procedure is performed by using forceps to remove the products of conception in multiple passes. Fetal demise can occur during the procedure by interrupting the umbilical cord, or feticidal agents can be used preoperatively through an injection of digoxin either transabdominal or transvaginally to ensure demise prior to the procedure. Complications for dilation and evacuation (D&E) increase with gestational age and other factors (previous cesarean section, obesity, inadequate cervical dilators). Most D&Es can be safely performed in an outpatient setting; however patients who have a high hemorrhage risk (suspected accreta) or other medical problems that place them at high risk of complications should be referred to a hospital setting.

11 Conclusion

Providers should be well versed in the contraceptive options available to women. A patient's medical history, desire for future fertility, and quality of menses will guide both the patient and her provider to make the appropriate choice. Long-acting reversible contraceptive options are particularly encouraged for women who desire future fertility, given their safety profile and convenience of use for the patient. The CDC phone "app" referring to the US Medical Eligibility Criteria for Contraceptive Use, 2010, is an additional resource available to providers.

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Preconception Care: In the Continuum of Women's Healthcare

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Abstract

The goals of preconception care are (1) to identify potential risks to the mother, fetus, and pregnancy, (2) to educate the women about these risks and provide options for intervention and management, and (3) to initiate interventions to provide optimal maternal, fetal, and pregnancy outcomes. Preconception counseling involves interventions that include health education and counseling related to reproductive risks and optimizing the control of medical disorders. If pregnancy is not desired, then contraceptive options should be discussed as preconception care begins with family planning to optimize the timing and intention of pregnancy. As such, all reproductive-age women should develop a reproductive health plan. Evidence supports an association between preconception counseling and positive changes in maternal behavior before and during pregnancy.

Keywords

Preconception counseling • Preconception • Reproductive life plan • Conception • Pregnancy • Teratogen • Obstetrics

1 Introduction

Preconception care is primary prevention and a preconception appointment is an integral first step toward a healthy pregnancy. The goal of preconception counseling is the reduction of potential harm and the recognition of modifiable risk factors related to pregnancy. Most pregnancies are uncomplicated with favorable maternal and fetal outcomes. However, optimizing health literacy before conception allows a woman to further reduce risk. More so, preconception care stratifies pregnancies on a continuum of low to high risk and allows women who could benefit from early intervention to possibly reduce pregnancy complications and/or birth defects. The early initiation of care relies on counseling about potential pregnancy risks and preventative strategies that are provided **before** conception.

Preconception counseling should be incorporated into any visit with a reproductive-age woman, as nearly half of all pregnancies in the United States are unplanned (Henshaw 1998). The challenge of preconception care lies in addressing pregnancy planning for women who seek any medical care and to screen and educate all reproductively capable women on an ongoing basis to identify potential maternal and fetal risks and hazards to pregnancy before and between pregnancies.

1.1 Definition and Rationale of Preconception Care

The Centers for Disease Control and Prevention (CDC) has defined preconception care as "a set of interventions that aim to identify and modify medical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management" (Johnson et al. 2006). In addition, they define the following goals for improving preconception care:

1. Improving the knowledge, attitudes, and behaviors of women related to preconception health.
2. Assure that all reproductive-age women receive preconception care, including evidence-based risk screening, health promotion, and interventions that will enable them to enter pregnancy in optimal health.
3. Reduce risks indicated by a previous adverse pregnancy outcome through preconception interventions to prevent or minimize recurrent adverse outcomes.
4. Reduce the disparities in adverse pregnancy outcomes.

Preconception care begins with family planning to optimize timing and intention of pregnancy. To assess the effectiveness of preconception counseling to increase planned pregnancies and reduce unintended pregnancies, the effects of a preconception care program instituted in a low-income health department clinic were reviewed (Moos et al. 1996). Over

Table 1 Core consideration during preconception counseling

Core considerations addressed during preconception counseling include, but are not limited, to the following:	
1.	Reproductive life plan
2.	Family history
3.	Maternal genetic conditions
4.	Infections and immunizations
5.	Chronic medical conditions
6.	Medications
7.	Environmental exposures
8.	Weight
9.	Nutrition
10.	Age
11.	Assisted reproductive technologies
12.	Social and lifestyle issues

400 women who were given preconception counseling demonstrated a 50% greater likelihood of their subsequent pregnancies being intended, compared with women who received healthcare but no counseling, and a 65% greater likelihood compared with women with no healthcare or counseling prior to pregnancy.

Optimizing maternal health and nutritional status prior to pregnancy and early gestation is important because organogenesis begins within weeks of fertilization. By the time most women realize they are pregnant, 1–2 weeks after the first missed period, organogenesis has started and many prevention strategies, such as folic acid to prevent neural-tube defects (NTDs) or glycemic control to prevent adverse pregnancy outcomes, are suboptimal in effect even if initiated ACOG (2005).

Several organizations have focused on the optimization of health before conception, resulting in the development of clinical recommendations and educational materials available for providers and patients (see Table 1) (see http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/The-Importance-of-Preconception-Care-in-the-Continuum-of-Womens-Health-Care#resources).

2 Reproductive Life Plan

To encourage preconception planning, the CDC offers a tool for healthcare professional to encourage patients to think about their reproductive goals and make a plan to facilitate these goals (http://www.cdc.gov/preconception/documents/rlphealthproviders.pdf). At every medical encounter, providers should ask a series of questions to formulate a reproductive life plan:

Questions to ask your patient: **Do you plan to have any (more) children at any time in your future?** *Open-ended question that allows branching.*

If They Answer YES

1. **How many children would you like?** Encourages woman to consider that there are choices about the number of children she has.
2. **How long would you like to wait until you or your partner become pregnant?** Encourages a woman to visualize her own future. Short interpregnancy intervals are associated with adverse fetal outcomes, including low birth weight and preterm birth.
3. **What family planning method do you plan to use until you or your partner are ready to become pregnant?** Gives the woman an opportunity to formulate a personal strategy. Slightly more than half of unintended pregnancies occur among women who were not using any method of contraception in the month they conceived.
4. **How sure are you that you will be able to use this method without any problems?** Encourages the woman to match her method choice to her lifestyle. Contraception can be highly effective if used appropriately; however, no method is perfect. In addition to nonuse of contraception, unintended pregnancies occur due to imperfect use of contraception (43%) and method failure (5%) (Frost et al. 2008).

If They Answer NO

1. **What family planning method will you use to avoid pregnancy?** Gives an opportunity to formulate and communicate a personal strategy to achieve plan.

2. **How sure are you that you will be able to use this method without any problems?** Encourages recognition that methods can have problems and to consider matching method choice to personal circumstances.
3. **Peoples' plans change. Is it possible that you or your partner could ever decide to become pregnant?** Relays the message that plans can change and that it is okay, but deliberate decisions about becoming pregnant are possible and desirable.

Action plan: Creating a reproductive health plan requires an ongoing conscientious assessment of the desirability of a future pregnancy, determination of steps that need to be taken either to prevent or to plan for and optimize a pregnancy, and evaluation of current health status and other issues relevant to the health of a pregnancy.

If pregnancy is not desired, current contraceptive use and options should be discussed to identify the most appropriate and effective method for her. Preconception and interpregnancy care are components of a larger healthcare goal that optimizes the health of every woman.

2.1 Components of Preconception Counseling

The first task of preconception counseling is obtaining a thorough history. There are several questionnaires and forms available for this purpose. Of special note in the history is a very thorough gynecologic and obstetrical history, which is essential to a preconception visit. For example, a detailed history of sexually transmitted infections, current medication use, and uterine malformations may decrease the risk of recurrent pregnancy loss. In a woman with a previous stillbirth, a detailed medical and obstetrical history, evaluation of previous stillbirth, and understanding of recurrence risk may help in the management of subsequent pregnancy. Additionally, reviewing the menstrual history is an opportunity to evaluate a woman's knowledge of menstrual physiology, determine endocrinologic comorbidities, and offer counseling about how she might plan a pregnancy.

3 Family History

Family history plays a critical role in assessing the risk of inherited medical conditions and single gene disorders. The US Surgeon General's Family History Initiative was launched in 2004 with the goal of educating healthcare providers and patients about the value of using a family history as a screening tool in clinical care (Yoon and Scheuner 2004). The preconception consultation is an optimal time to review the family history and discuss the option of undergoing carrier screening for genetic conditions. It is important to obtain the family history of both the patient and her partner, including their ethnic backgrounds, and any adverse pregnancy outcomes as a couple, or with other partners. Positive responses will need to be followed up by appropriate risk assessment, testing, and genetic counseling if needed (Table 2).

Any genetic counseling and testing that can be completed before conception is beneficial to the couple, and allows a broader array of options and greater time for decision-making. Some communities with high prevalence of carrier status even advocate for testing prior to considering pregnency (JGDC 2015). Because of counseling, couples may decide not to conceive, or they may consider using an egg donor or obtaining a preimplantation genetic screening. A patient who has had a past adverse pregnancy outcome or has a family history of other adverse pregnancy outcomes might be at increased risk of these disorders. Because both genetic and environmental factors may contribute to some of these outcomes, advising a patient that she is at increased risk of an adverse pregnancy outcome based on family history might motivate her to reduce her environmental risk (Dolan and Moore 2007).

Table 2 Red flags for genetic conditions (2011; NCHPEG 2015)

Family history of a known or suspected genetic condition
Ethnic predisposition to certain genetic disorders
Consanguinity
Multiple affected family members with the same or related disorders
Earlier than expected age of onset of disease
Diagnosis in less-often-affected sex
Multifocal or bilateral occurrence of disease (often cancer) in paired organs
Disease in the absence of risk factors or after application of preventive measures
One or more major malformations
Developmental delays or mental retardation
Abnormalities in growth
Recurrent pregnancy losses

Table modified from Family history as a risk assessment tool. Committee Opinion No. 478. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:747–50

4 Maternal Genetic Conditions

Patients with genetic conditions will benefit from a preconception evaluation with their obstetrician, geneticist, maternal–fetal medicine (MFM) specialists, or appropriate subspecialists to optimize their care. Precise identification of maternal genetic conditions in the preconception period is important to review maternal health risks and offspring morbidities associated with pregnancy, to counsel the patient regarding mode of inheritance, partner carrier screening, assessment of genetic condition risk in the offspring, and the availability of prenatal diagnosis or preimplantation genetic screening (Table 3). The need for a multidisciplinary approach to care will vary with the patient's condition, but all patients should create a plan that addresses possible adverse effects of a pregnancy on the condition and of the condition on a pregnancy.

For some genetic conditions associated with significant maternal morbidity and mortality, consideration should be given to avoiding pregnancy altogether and providing appropriate family planning, contraception counseling, and viable alternatives via assisted reproductive technologies (ART) (e.g., donor gametes or surrogacy). Patients with complex medical conditions may require treatment with medications that have potential teratogenic effects. Patients should be counseled that medications should not be discontinued until a thorough discussion with the appropriate members of the multidisciplinary team has been done to review the risks, benefits, and therapeutic alternatives. In some circumstances, the treatment adjustments need to be made before conception to minimize reproductive risks. Patients with established causative mutations for a genetic condition, and who desire prenatal genetic testing, should be offered preimplantation genetic screening with in vitro fertilization (IVF) by a reproductive endocrinologist or prenatal diagnostic testing after pregnancy is established.

5 Infections and Immunizations

Certain infections during pregnancy can cause **birth defects** and pregnancy complications. Many infections can be prevented by proper immunizations or education on hygiene. Preconception immunization of women to prevent diseases is generally preferred to vaccination in pregnancy; however, only live-virus vaccines can be of any theoretical risk to the fetus.

Two vaccinations are of particular importance while planning for and during pregnancy: influenza and pertussis. **Influenza** can cause significant morbidity and mortality in pregnancy. It is therefore critically important that all providers of reproductive-age women advocate for influenza vaccination, provide the influenza vaccine to their pregnant patients, and receive the influenza vaccine themselves every season ACOG (2014). Influenza vaccines should be given in inactivated, single-dose, intramuscular form during pregnancy. Women planning pregnancy should also be counseled on the importance of receiving a dose of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine during *each* pregnancy, ideally between 27 and 36 weeks' gestation. Lastly, women are often immune to measles, mumps, and rubella

Table 3 Overview of select maternal genetic conditions in pregnancy

Genetic condition	Mode of inheritance	Key features
Pulmonary		
Cystic fibrosis	Autosomal recessive	Sinopulmonary disease, obstructive lung disease, recurrent infections, gastrointestinal and nutritional deficiencies, obstructive azo0spermia, salt-loss syndromes, diabetes, and pancreatic insufficiency
Cardiac		
Marfan syndrome	Autosomal dominant	Aortic root enlargement with risk of dissection; mitral valve prolapse; ectopia lentis; myopia; skeletal manifestations, including joint laxity and pectus abnormalities; dural ectasia; and lung bullae
Neurocutaneous		
Neurofibromatosis type 1	Autosomal dominant	Café au lait spots, inguinal and axillary freckling, neurofibromas, Lisch nodules, learning disabilities, scoliosis, and optic nerve and central nervous system gliomas
Tuberous sclerosis	Autosomal dominant	Skin abnormalities – hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, and ungual fibromas Bran findings – cortical tubers, subependymal nodules, and seizures Kidney issues – angiomyolipomas, cysts, and renal cell carcinomas Heart and lung issues – rhabdomyomas, arrhythmias, and lymphangioleiomyomatosis
Renal		
Autosomal dominant polycystic kidney disease	Autosomal dominant	Renal cysts; liver and other organ cysts; vascular malformations, including intracranial aneurysms; abdominal wall hernias; hypertension; renal insufficiency; aortic root dilation with risk of dissection; and mitral valve prolapse
Metabolic		
Classic phenylketonuria (PKU)	Autosomal recessive	Children born to women with PKU on unrestricted diets at risk of intellectual disability, microcephaly, and congenital heart defects Universal newborn screening for PKU in the United States Before conception, patients should consume a low-protein diet and use a phenylalanine-free medical formula to achieve plasma phenylalanine concentrations of 120–320 μmol/L
Noonan syndrome	Autosomal dominant	Short stature; characteristic facial features; congenital heart defects, including pulmonic stenosis, lymphatic dysplasias; intellectual disability of varied degree; pectus deformity; varied coagulation defects; and renal abnormalities
Myotonic dystrophy type 1	Autosomal dominant – trinucleotide repeat disorder	Three types: 1. Mild (cataract and mild myotonia) 2. Classical (muscle weakness, myotonia, cataracts, and cardiac conduction abnormalities) 3. Congenital (severe hypotonia, respiratory failure, intellectual disability, and early death)

Table modified from Identification and Referral of Maternal Genetic Conditions in Pregnancy. Committee Opinion No. 643. American College of Obstetricians and Gynecologists. 2015 Oct;126(4):e49–51

(MMR), poliomyelitis, and varicella through childhood-conferred immunization or exposures.

The increased understanding of the link between Zika virus and fetal neurological effects adds another discussion to preconception counseling. Since the rate of vertical transmission is not known, the CDC recommends that women diagnosed with Zika, or who have had possible

exposure, wait at least 8 weeks after their exposure or onset of symptoms before attempting conception. Male partners should wait at least 6 months after their symptoms to have unprotected intercourse (Petersen et al. 2016). Women residing in endemic areas are currently encouraged to possibly delay pregnancy, after a reproductive life plan discussion with a physician knowledgeable about Zika (Simeone et al. 2016).

Immune globulin or vaccination against poliomyelitis, yellow fever, typhoid, or hepatitis may be indicated for travels to endemic areas.

Additional infectious disease screening includes:

1. **Rubella**: Screening for anti-rubella IgG identifies rubella nonimmune women who should be offered vaccination. If serologic testing demonstrates that they are susceptible, women should be vaccinated with rubella vaccine before conception occurs. If preconception counseling is not possible, patients should have serologic testing to document rubella immunity status at the time of their first prenatal appointment. Women who are susceptible to rubella should be counseled to avoid exposure to other individuals who may have viral exanthems.
2. **Hepatitis B**: Universal screening of pregnant women for hepatitis B virus has been recommended by the CDC since 1988. Women with social or occupational risk for exposure to hepatitis B, such as healthcare providers, should be counseled and offered vaccination.
3. **Pneumococcus**: The pneumococcal polysaccharide vaccine is recommended for all adults with conditions that increase the risk of invasive pneumococcal disease, which includes immunocompetent women with underlying health conditions (chronic heart, lung, or liver disease, diabetes mellitus, alcoholism, cochlear implants, and cigarette smoking), anatomic asplenia, and immunocompromised persons. Ideally, this vaccine would be given preconceptionally, but the indications for administration are not different in pregnancy.
4. **Tuberculosis**: Patients at risk for tuberculosis should be tested with a subcutaneous purified protein derivative (PPD) challenge. If the patient has a history of bacillus Calmette-known-positive skin testing, quantiferon-Gold can be used as an alternative. Preconception treatment for latent TB infection can be ordered as indicated.
5. **Parvovirus B19:** Parvovirus IgG testing may be offered preconceptionally to teachers and childcare workers.
6. **Chickenpox**: Screening for varicella IgG should be performed if a positive history of prior chickenpox cannot be obtained. The varicella zoster virus vaccine is now recommended for all nonimmune adults. The VZV vaccine is a live-virus vaccine that should be given at least 30 days prior to conception. Nonimmune women can be counseled regarding postexposure prophylaxis during pregnancy.
7. **HIV**: ACOG recommends that all pregnant women should be screened for **HIV** infection as early as possible during each pregnancy using the opt-out approach. Repeat HIV testing in the third trimester is recommended for women in areas with high HIV incidence or prevalence and women known to be at risk of acquiring HIV infection ACOG (2015). If the diagnosis of HIV infection is established, the woman should be linked into ongoing care with a specialist in HIV care for comanagement.
8. **Sexually transmitted infections**: Sexually transmitted infections (STIs) can affect women's ability to become pregnant and cause infections that affect pregnancy outcomes. Common STIs are chlamydia, gonorrhea, genital herpes, trichomoniasis, hepatitis B, and syphilis, and HIV. Testing for STIs before pregnancy gives the women the opportunity to possibly avoid a poor pregnancy outcome. Preconception testing for the following STIs is currently recommended for all: HIV, as above, and chlamydia and gonorrhea for women 25 years or younger or if they are older than 25 years with risk factors. A wider panel of STIs, including syphilis and

hepatitis C, can be tested in women at high risk, such as sex workers or intravenous drug abusers.

6 Chronic Medical Conditions

Preconception care should include an ascertainment of medical conditions. Obtaining consultation and ongoing close collaboration with other specialist may be indicated. Briefly, some common or serious medical conditions that impact or are impacted by pregnancy are discussed below by system.

1. **Neurologic**

   Seizure disorders. Seizure disorders are the most common neurologic disease to affect pregnant women, and both the disease and its treatments can adversely affect pregnancy. Approximately one-third of women with a seizure disorder will experience more frequent seizures in pregnancy. Poorly controlled seizure disorder has been associated with miscarriages, low birth weight, developmental disabilities, microcephaly, and hemorrhagic disease of the newborn (Hadar et al. 2015). Seizure disorders increase the risk of congenital anomalies, whether or not the mother is taking antiepileptic drugs (AEDs). Generally, obstetricians and neurologists will recommend that patients planning pregnancy should be managed on the most effective AED, ideally monotherapy at the lowest possible drug dose, for their seizures and will not make changes to AEDs for the purpose of reducing teratogenic risk with the exception of valproate. Low folate levels in women with epilepsy are associated with an increased risk of major fetal malformations. Furthermore, given the increased rates of NTDs with many AEDs, supplementation with 4.0 mg of folic acid (versus 0.4 mg recommended to all women of childbearing potential) should be initiated at least 1 month before conception and continued in the first trimester in women with a seizure disorder.

   Multiple sclerosis. Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the CNS typically characterized by relapses and remissions of neurologic deficits. MS occurs with a 3:2 ratio of females to males and a peak incidence of 30 years of age. Fortunately, pregnancy does not appear to affect the type or severity of exacerbation and may even have a protective effect against relapses. However, higher rates of relapse in the postpartum period have been reported. Long-term disability due to MS is not altered by pregnancy. There are no accepted guidelines for recommending for or against pregnancy in women with MS, and each patient's MS history and current neurologic deficits should be considered independently. A multidisciplinary approach is required, combining the expertise of MFM and neurology. Medication adjustments may be recommended prior to pregnancy.

2. **Cardiovascular**

   Hypertension. Chronic hypertension affects 3–5% of women of reproductive age ACOG (2015). Hypertension is a common comorbidity of diabetes and is found in 20–30% of women who have had diabetes for longer than 10 years. Chronic hypertension in pregnancy is associated with higher rates of preterm birth, placental abruption, intrauterine growth restriction, preeclampsia, and fetal demise. Women with chronic hypertension are at risk of worsening hypertension and end-organ damage, and 20–25% of women with hypertension develop superimposed preeclampsia during pregnancy. Treating severe hypertension (systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher) improves pregnancy outcomes (Sibai and Anderson 1986), but goal blood pressure range remains contested. Caring for women of reproductive age with hypertension should include educating them about the risks of hypertension during pregnancy.

   Women with long-standing hypertension who are planning pregnancy should be assessed for retinopathy, renal disease, and

ventricular hypertrophy. Blood pressure medications that are safe for pregnancy should be added sequentially until target blood pressure levels are achieved. Such agents include long-acting calcium channel blockers, selected beta-adrenergic blockers, and methyldopa. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are contraindicated in pregnancy because of associated teratogenicity. Women treated with these agents should use effective contraception or be converted to safer agents prior to conception. Women taking statins should also be advised to discontinue them under the guidance of a provider.

Congenital cardiac disease: As more women with congenital cardiac disease, both corrected and uncorrected, reach reproductive age, preconception counseling and family planning for this unique category of women becomes increasingly important. Pregnancy and its associated changes in cardiovascular physiology can pose significant risks to women with congenital heart disease. These women require a multidisciplinary approach with both cardiology and MFM preconceptionally.

3. **Pulmonary**

Asthma. Asthma complicates approximately 4–8% of pregnancies (Kwon et al. 2003). Women with poorly controlled asthma before pregnancy and at conception are more likely to experience worsening symptoms with pregnancy. The goal of asthma treatment in pregnancy is to maintain adequate oxygenation of the fetus by preventing hypoxic episodes in the mother (Dombrowski and Schatz 2008). Preconception care should focus on optimizing asthma control with medications, and identifying and reducing exposure to allergens. Patients should be counseled on smoking cessation and avoidance of secondhand smoke exposure. Asthma self-management skills, including self-monitoring with peak flow monitors, correct use of inhalers, and following a plan for long-term management of asthma and promptly handling signs of worsening asthma enhances asthma control. Inhaled corticosteroids are first-line controller therapy for persistent asthma during pregnancy. Influenza vaccination is of even more importance in women with asthma as concomitant infectious comorbidity can lead to significant respiratory decompensation.

4. **Gastroinsteninal**

Inflammatory bowel disease. Women with inflammatory bowel disease (IBD) (Crohn's disease and ulcerative colitis), should address disease control, medications, and nutritional status preconceptionally as IBD affects women in their reproductive years. IBD does not decrease fertility; however, fertility in patients with IBD is possibly affected by active disease, medications, and prior surgeries. Women with IBD may experience worse obstetrical and pregnancy-related outcome compared to the general population, even with the disease in remission (Cornish et al. 2007). As such, optimizing the preconception disease burden can attenuate risk. The course of IBD during pregnancy is determined by the activity of the disease at conception. Hence, patients in remission at the time of conceptions are likely to remain in remission during pregnancy. In contrast, up to 70% of women with active disease at conception will have continued or worsening symptoms (Getahun et al. 2014). The choice of anti-inflammatory and immunosuppressive medications during pregnancy should be based on the safety profile of the medication, as well as the risk of relapse of IBD if the medication is discontinued.

5. **Renal**

Lupus nephritis. Women with systemic lupus erythematosus (SLE), particularly lupus nephritis, have a better pregnancy prognosis if their disease has been quiescent for at least 6 months prior to pregnancy and they have normal or near-normal renal function. Active SLE at the time of conception is a strong predictor of adverse maternal and obstetrical outcomes. Disease flares with pregnancy are difficulty to decouple from the physiologic changes of pregnancy versus disease hallmarks. Most SLE medication can be continued during pregnancy, but some (such as some

anti-inflammatories and methotrexate) will need to be discontinued under the guidance of a physician. The most important aspects of preconception counseling with SLE is to determine whether pregnancy may present an unacceptable high maternal or fetal risk to optimize interventions that can decrease risk, and to adjust medications that are known to be harmful to the fetus.

6. **Hematological and immune**

   Thrombophilia. Confirmed inherited or acquired thrombophilia places women at a higher risk of thromboembolic complications during pregnancy because of the inherent hypercoagulable state of pregnancy. These coagulation factor changes include resistance to activated protein C in the second and third trimester; decrease in protein S activity due to a reduction in total and free protein S antigen; increase in fibrinogen and factors II, VII, VIII, and X; and increases in levels and activity of fibrinolytic inhibitors, thrombin fibrinolytic inhibitor, and plasminogen activator inhibitor (Lockwood 1999). The goal of screening and treatment of appropriate women with specific inherited thrombophilias is the prevention of maternal venous thromboembolism (VTE). Risk and treatment of VTE depend on the type of inherited thrombophilia and a personal or family history of thrombosis. Preconceptional consultation with hematology and MFM is recommended.

7. **Endocrine**

   Diabetes. The goal of preconception diabetes management is to achieve a glycosylated hemoglobin (A1c) level within the normal range before conception, in order to prevent or minimize the postconception sequelae of diabetes: miscarriage, congenital anomaly, macrosomia, polyhydramnios, preterm labor, shoulder dystocia, birth injury, and postnatal metabolic instability of the newborn. A secondary goal is to reduce the risks associated with in utero fetal programming, including future pediatric and adult metabolic syndrome in the offspring. For this goal to be achieved, glycemic control must be instituted early and aggressively (Bellamy et al. 2009), and appropriate contraception would ideally be used until the patient is ready.

   Diabetes affects nearly 10% of women of reproductive age, and about 1% of pregnancies are complicated by pregestational diabetes (Bellamy et al. 2009). Glucose is known to be teratogenic at high levels, and rates of congenital fetal anomalies are directly related to glycemic control in the first trimester. Optimal glycemic control during organogenesis reduces rates of congenital malformations. Pregnancy and associated nausea and vomiting can also lead to higher rates of hypoglycemia, decreased hypoglycemic awareness, increased rates of diabetic ketoacidosis, and the progression of diabetic retinopathy and nephropathy (Metzger et al. 2008).

   Preconception counseling improves pregnancy outcomes in women with diabetes and should include educating women about the impact of diabetes on pregnancy outcomes and the impact of pregnancy on diabetes, optimizing glycemic control, screening for vascular complications of diabetes, evaluating medication use, and encouraging effective family planning. For patients who have had diabetes for 10 years or longer, evaluation for baseline electrocardiogram, echocardiogram, microalbuminuria, and serum creatinine should be considered. Because microvascular disease can progress during pregnancy, ophthalmic and podiatric examinations are also recommended.

   Thyroid disease. Thyroid disease can significantly impact pregnancy outcomes, as uncontrolled thyrotoxicosis and hypothyroidism are associated with adverse pregnancy outcomes. Hypothyroidism affects 2.5% of women of reproductive age. Hypothyroidism in the first trimester is associated with cognitive impairment in children. Hypothyroidism in pregnant women increases the risk of preterm birth, low birth weight, placental abruption, and fetal death (Fitzpatrick and Russell 2010).

   Women who are adequately treated before pregnancy and those diagnosed and treated early in pregnancy have no increased risk of

perinatal morbidity. It is essential to monitor women on thyroid replacement therapy. During pregnancy, thyroid replacement dosages typically need to be increased every 4–6 weeks' gestation, possibly by 30% or more. Universal screening for thyroid disease in pregnancy is not recommended because identification and treatment of maternal subclinical hypothyroidism has not been shown to result in improved neurocognitive function in offspring ACOG (2005). The first-line screening test used to assess thyroid status in patients at risk is measurement of the TSH level.

Hyperthyroidism can result in significant maternal and neonatal morbidity, and outcomes correlate with disease control (Stagnaro-Green and Pearce 2012). Patients with Graves' disease should be evaluated for the presence of thyroid-stimulating immunoglobulins.

8. **Mental health**
   Depression. Approximately 10–15% of women of reproductive age are affected by depression. Untreated mood disorders in pregnancy can be potentially serious, with approximately 40–50% of untreated patients experiencing an episode of decompensation and 15% are at risk for suicidal ideation. Untreated depression may increase the risk of adverse pregnancy outcomes, such as stillbirth, IUGR, preterm delivery, low Apgar scores, STIs, and substance abuse. Patients should be counseled that the risk of uncontrolled psychiatric disease typically outweighs the theoretical risk of medications during pregnancy, and therefore medications should be continued if medically indicated. Close co-surveillance with her mental health provider is important before, during, and after pregnancy.
9. **Oral**
   Dental disease: Pregnancy may results in physiological changes in the oral cavity: pregnancy gingivitis, tooth mobility, tooth erosion, dental caries, and periodontitis (ACOG 2013). Dental caries and periodontal diseases are common and may be associated with pregnancy complicates, such as preterm delivery; thus, referral to a dentist is appropriate. Patients should be reassured that prevention, diagnosis, and treatment of oral health conditions, including shielded dental X-rays and local anesthesia, are safe during pregnancy. Delaying treatment could result in more complex problems. Preconception counseling and evaluation by dentist is a good time to reinforce oral health maintenance such as fluoridated toothpaste for brushing twice a day, flossing, limiting sugary drinks, and dental visits twice a year.

7 Medications

The woman's preconception medications should be reviewed and altered to avoid teratogenicity, when clinically appropriate and feasible. Evaluation of exposure to medications includes over-the-counter and prescription medications, herbs, and supplements. Of note, in December 2014, the FDA published the Pregnancy and Lactation Labeling Rule or final rule (PLLR), which changed the labeling requirements for prescription drugs. This removed the pregnancy letter categories and created descriptive subsections for pregnancy exposure and risk, lactation, and effects to reproductive potential. Labeling changes began in June 2015, for all new drug submissions. Previously approved drugs will gradually switch to the new labeling. The rule does not affect over-the-counter drug labeling.

Since the conversion to the PLLR labeling has not yet fully taken effect, we will discuss medications using the standing terminology. Traditionally, FDA pregnancy categories X and D should be avoided.

Important medications to discuss include:

1. **Statins**: Category X. Should be discontinued before conception.
2. **Isoretinonin**: Category X. Should be discontinued before conception.
3. **Warfarin**: Category X. Should be discontinued before conception except with a mechanical heart valve.
4. **ACE inhibitors and ARBs**: Category C in first trimester and category D in second and

third trimesters. Should be discontinued before conception.

5. **Oral anti-glycemic agents**: Metformin and acarbose are classified as category B, although systematic data on safety are lacking. All other agents are category C drugs. The potential risks and benefits of oral antidiabetic agents in the preconception period should be carefully weighed.
6. **Antiepiletic drugs (AEDs)**: Valproate (category D) is associated with neural-tube defects as well as craniofacial, limb, and cardiac abnormalities. Carbamazepine (category D) exposure has been associated with facial dysmorphism and fingernail hypoplasia. Data on second-generation AEDs are still limited. Women should continue AEDs that control their epilepsy, ideally as a monotherapy at the lowest effective dose.
7. **Psychotropic medications**: Some psychiatric medications are of concern for teratogenesis; however, untreated psychiatric illness is also associated with poor pregnancy outcomes, including premature birth, low birth weights, and fetal growth restriction. Treatment of bipolar disorder with lithium has been associated with increased incidence of heart defects. During pregnancy, a fetal echocardiogram is recommended for women taking lithium in the first trimester. Most selective serotonin reuptake inhibitors (SSRIs) are considered safe; however, paroxetine early in pregnancy has been associated with an increased risk of heart defects, and an FDA advisory notes a possible association between late-term SSRI use and persistent pulmonary hypertension in the newborn. SSRI use in pregnancy should be individualized, balancing the risks of maternal depression and potential fetal effects.
8. **Contraceptives**: No evidence indicates teratogenicity from oral contraceptive or contraceptive implant use.

Resources for Medications During Pregnancy

- LactMed www.toxnet.nlm.nih/gov/cgi-bin/sis/htmlgen?LACT
- OBPharmacopoeia: http://www.perinatology.com/Reference/OBPharmacopoeia-Public/PharmacopoeiaTOC-public.htm
- ReproTox: https://reprotox.org/
- Briggs Drugs in Pregnancy and Lactation textbook

Resources for Information on Potential Teratogens

- National Library of Medicine (NLM), sis.nlm.nih.gov/
- Reproductive Toxicology Center (ReproTox), www.reprotox.org
- Teratogen Information System (TERIS Catalog) http://depts.washington.edu/terisweb/teris/
- Organization of Teratology Information Specialists (OTIS), www.OTISPregnancy.org
- The Hospital for Sick Children, Toronto, Canada, http://www.motherisk.org/women/drugs.jsp
- Pediatric Environmental Health Specialty Units (PEHSU), www.pehsu.net/aboutus.html

8 Environmental Exposures

Questions about women's work, hobbies, pets, and home environment can identify potentially toxic exposures, such as mercury, pesticides, lead, and endocrine-disrupting chemicals (phthalates, bisphenol A, polybrominated diethyl ethers) (McDiarmid et al. 2008). In additional to occupational exposures, mercury may be found in fish and skin-lightening creams. Lead exposure can come from paint (pre-1970), imported cosmetics, food additives, medicine, and clay (Sathyanarayana et al. 2012). Exposure to outdoor cats and their fecal matter can increase risk of toxoplasmosis. These are all potential modifiable risk factors.

9 Weight

In the United States, 26% of women 20–39 years of age are overweight, defined as body mass index (BMI) of 25–29.9 kg/m^2, and prevalence rates

continue to rise. Obese (BMI above 30 kg/m^2) and underweight women (BMI <18.5 kg/m^2) are at risk for adverse pregnancy outcomes. Women who are overweight or obese are at risk of diabetes, gestational diabetes, hypertension, macrosomia, cesarean delivery, and thromboembolism. Low prepregnancy BMI is associated with preterm birth and low birth weight. Low body weight is also associated with nutrient deficiencies, osteoporosis, amenorrhea, infertility, and arrhythmias. Women with low BMIs should be assessed for eating disorders and counseled about how being underweight can affect their health and pregnancy (ACOG 2013). Nutritionist referrals may be beneficial.

Recommendations for obese (BMI >30 kg/m^2) women (ACOG 2013): Preconception counseling for obese women who are pregnant or planning a pregnancy includes the following:

- Preconception assessment and counseling
- Evaluation for sequelae of obesity
- Documentation of current and goal weight and BMI
- Provision of specific information concerning the maternal and fetal risks of obesity in pregnancy
- Encouragement to undertake a monitored weight-reduction program
- Nutrition consultation
- Evaluation for prior history of bariatric surgery or candidacy for bariatric intervention

9.1 Bariatric Surgery

Managing a patient who has had bariatric surgery ideally involves a planned pregnancy, coordination with the bariatric surgery team, and preconception nutritional counseling. Bariatric surgery is available for patients with a BMI >40 kg/m^2 (or >35 kg/m^2 with comorbidities) (Xanthakos and Inge 2006). The roux-en-Y gastric bypass (65%) or adjustable gastric banding (24%) (Xanthakos and Inge 2006) aims to cause weight loss by restricting food intake, food malabsorption, or both.

All bariatric surgery candidates should undergo contraceptive options and preconception counseling. Ideally, women will use contraception for the first 12–18 months postoperatively to minimize the pregnancy risk during the initial rapid weight loss period. Rare complications of bariatric surgery carried out during pregnancy include intestinal obstruction, gastrointestinal hemorrhage, hernias, anastomotic leaks, and band complications.

Screening for diabetes will also be potentially limited by dumping syndrome. In these patients with possible underlying insulin resistance, evaluation for pregestational diabetes or insulin resistance may help elucidate further pregnancy risk. At their preconception visit, women with a history of bariatric surgery should obtain a laboratory measure of baseline nutritional status which includes complete blood count (CBC), iron studies, albumin level, ferritin levels, vitamin B1 (thiamine) level, vitamin B12 level, calcium and phosphorus levels, and 25-hydroxyvitamin D levels. Additionally, it is important to appropriately treat nutritional deficiencies throughout pregnancy with close monitoring of weight changes. A caveat is that in the setting of restrictive surgeries, attention should be placed that any medication prescribed should ideally be less than 10 mm. A helpful patient handout:

http://contemporaryobgyn.modernmedicine.com/sites/default/files/images/ContemporayOBGYN/SMFM_bariatric_patient_handout.pdf

9.2 Weight Gain

The recommended weight gain for pregnancy is based on prepregnancy BMI. Pregnant women require 15% more calories than nonpregnant women, usually 300–500 kCal more per day, depending on the patient's weight and activity. The total weight gain recommended is 25–35 lb for women with a normal BMI. Underweight women may gain 40 lb or more, and overweight women should limit weight gain to <25 lb or less. Three to six pounds is typically gained in the first trimester, and 0.5–1.0 lb per week is gained in the last two trimesters of pregnancy. Inadequate weight gain is associated with an increased risk of low birth weight in infants. Total weight gain in

obese patients can be as low as 11 lb. Preconception education for ideal pregnancy weight gain and dietary changes can help set realistic expectations for intended mothers.

Institute of Medicine Weight Gain Recommendations for Pregnancy (2009, 2013)

Prepregnancy weight category	Body mass index	Recommended range of total weight (lb)	Recommended rates of weight gain† in the 2nd and 3rd trimesters (lb) (mean range [lb/wk])
Underweight	<18.5	28–40	1 (1–1.3)
Normal weight	18.5–24.9	25–35	1 (0.8–1)
Overweight	25–29.9	15–25	0.6 (0.5–0.7)
Obese	>30	11–20	0.5 (0.4–0.6)

10 Nutrition

Dietary allowances for most vitamins and minerals increase with pregnancy and are adequately supplied in a well-balanced diet. The recommendations listed below are for singleton gestations. Requirements need to be adjusted with multiple gestations. Increased iron is needed for both the fetus and the mother. Consumption of iron-containing foods should be encouraged, and iron supplements may be prescribed during pregnancy. The 30-mg elemental iron supplement is contained in approximately 150 mg of ferrous sulfate, 300 mg of ferrous gluconate, and 100 mg of ferrous fumarate. Prenatal calcium requirement is 1,200 mg per day.

After the establishment of a pregnancy, and during subsequent prenatal visits, nutrition should continue to be discussed as discussions revolve around the avoidance of unpasteurized cheeses and deli meats to avoid the risk of exposure to *Listeria monocytogenes.* Excess use of multivitamin and supplements containing vitamin A should be avoided because the estimated dietary intake of vitamin A for most women in the United States is sufficient. Vitamin A is teratogenic in humans at dosages of more than 20,000–50,000 IU daily. Women with a history of anorexia or bulimia may benefit from nutrition and psychological counseling before conception.

10.1 Folic Acid

The initiation of folic acid supplementation at least 1 month before pregnancy reduces the incidence of NTDs, such as spina bifida and anencephaly (Czeizel and Dudas 1992). Folic acid supplementation of 400 mcg (0.4 mg) daily started before pregnancy and continued until 6–12-week postconception reduces the rate of neural-tube defects by nearly 75%. Women receiving preconception counseling from their physicians are five times more likely to take folic acid before conception (Elsinga et al. 2008). Unless contraindicated by the presence of pernicious anemia, women who have previously carried a fetus with an NTD, have epilepsy, or are taking folic acid antagonist should take 4.0 mg of folic acid daily (Wilson et al. 2003).

11 Exercise

Conditioned pregnant women usually can continue to exercise throughout gestation, with appropriate modifications (ACOG 2002). There are no data to suggest that exercise is deleterious during pregnancy. One caveat is that as pregnancy progresses, balance problems and joint relaxation may predispose to orthopedic injury. A woman should be advised not to exercise to exhaustion, and she should augment heat dissipation and fluid replacement. She should avoid supine positions, activities requiring good balance, and extreme weather conditions. In the absence of obstetric or medical complications, moderate physical activity can maintain cardiovascular and muscular fitness throughout pregnancy and the postpartum period. No data suggests that moderate aerobic exercise is harmful to the mother or fetus. Certain obstetric complications may lead to recommendations to further modify or decrease activity, and these will be determined by her obstetrics provider during the pregnancy.

12 Age

In the United States, 10% of pregnancies occur in women after 35 years of age. Older woman are more likely to obtain preconceptional counseling. After age 35, there is an increased risk for obstetrical complications, chromosomal abnormalities, and perinatal morbidity and mortality (Cunningham and Leveno 1995). Older women with multiple chronic medical conditions or who are in poor physical condition usually have readily apparent risks. For the physically fit woman without medical problems the risks are much lower. Fetal risks associated with advanced maternal age stem primarily from (1) indicated preterm delivery for maternal complications such as hypertension and diabetes, (2) spontaneous preterm delivery, (3) fetal growth disorders related to chronic maternal disease or multifetal gestation, (4) fetal aneuploidy, (5) increased risk of multiple gestations, and (6) pregnancies resulting from use of ART. Most researchers have found that fetal aneuploidy is the only congenital abnormality related to maternal age.

13 Assisted Reproductive Technologies

About 1% of births in the United States are a result of ART (Wright et al. 2005). Couples with fertility problems (10% of couples in the developed world) seeking treatment with ART should receive the same baseline preconception counseling as women without fertility problems. Underlying disorders leading to primary or secondary infertility, such as congenital Müllerian anomalies, endocrinologic abnormalities, or recurrent pregnancy loss, may require more focused preconception counseling. Additional counseling should address ART success rates and the possible risks associated with ART. As reviewed above, a woman's age decreases her success of achieving a live birth after 35 years old, with decreasing ovarian reserve. This holds true for ART. Singleton gestations conceived by ART may have lower birth weights and possibly carry an increase in imprinting disorders (Camprubi et al. 2013) and congenital cardiac anomalies. The major risk of ovarian stimulation (clomiphene citrate and letrozole) is multiple gestations. About one-third of live births delivered by ART have more than one infant, and twins represent 85% of these multiple-birth children (Grainger et al. 2006). There are more complications in multiple gestations, which include the morbidities associated with preterm delivery. The risks of higher-order multiples should be discussed prior to ART therapy, including the patient and partner's preferences for selective reduction procedures.

14 Social and Lifestyle History

A detailed social and lifestyle history should be obtained to identify potentially risky behavior and exposures that may compromise pregnancy outcome and to identify social, financial, and psychological issues that could affect pregnancy planning.

All patients should be asked about alcohol, tobacco, and other drug uses:

1. **Alcohol** is a known teratogen, and a clear dose-response relationship exists between alcohol use and fetal effects. The American Academy of Pediatrics identifies prenatal exposure to alcohol as the leading preventable cause of birth defects and intellectual and neurodevelopmental disabilities in children and recommends complete abstinence from alcohol during pregnancy (Williams and Smith 2015).
2. **Marijuana** is the illicit drug most commonly used during pregnancy, with estimated prevalence rates of 2–5%. Cannabinoids have been associated with impaired neurodevelopment and emotional dysregulation, and women should be encouraged to discontinue prior to pregnancy (2015).
3. **Cocaine** has also been identified as a teratogen, as well as a cause of prematurity, abruptio placentae, and intrauterine growth restriction.
4. **Tobacco** use has been identified as the leading preventable cause of low birth weight. At least 11% of pregnant women in the United States

smoke. Nicotine is considered teratogenic and a modifiable lifestyle with extensive counseling on smoking cessation, intensive smoking reduction program, and nicotine replacement therapy. If substance addiction is present, a structured recovery plan is needed to effect behavioral change.

Pregnancy can exacerbate interpersonal problems and is a time of increased risk from an abusive partner. Victims of domestic violence should be identified before they conceive. They are most likely to be abused during pregnancy than at other times. Approximately 37% of abused women are assaulted during their pregnancy, resulting in possible abruptio placentae, antepartum hemorrhage, fetal fractures, rupture of internal organs, and preterm labor. Information about community, social, and legal resources should be made available to women who are abused and a plan devised for dealing with an abusive partner.

The preconception interview is also an appropriate time to discuss insurance coverage and financial difficulties. Many women and couples do not know their eligibility or may lack medical insurance coverage altogether. Referral for medical assistance programs, such as the Women, Infants, and Children's (WIC) program, should be part of preconception planning. WIC is a supplemental food and nutrition program for pregnant women, new moms, and children under the age of five. Through the WIC program, women receive financial assistance in purchasing food, counseling and information on health eating, breastfeeding support, and information and referrals to health and community resources. WIC state agency contacts are available at http://www.fns.usda.gov/wic-state-agency-contacts.

15 Cancer Survivors

Pregnancy risks for women who are cancer survivors vary based on the cancer and the treatment received. For example, a woman who has been on a cardiotoxic chemotherapy (i.e., adriamycin) or has received chest radiation needs an assessment of her cardiac function prior to pregnancy. Preconception evaluation should be modified based on oncological therapy. Baseline liver and renal function tests should be performed, as chemotherapy can be hepatotoxic and/or nephrotoxic. Prior chemotherapy and radiation do not confer any increased risk of adverse pregnancy outcomes, genetic conditions, or childhood cancers (Green et al. 2002). However, prior radiation to the abdomen and pelvis has been associated with an increased rate of miscarriage and poor pregnancy outcomes (Signorello et al. 2010). There is an increased risk of cancer in the offspring of women with hereditary cancer syndromes, such as BRCA or hereditary nonpolyposis colorectal cancer. These women should have a preconception visit with a genetic counselor.

Young women who may be receiving chemotherapeutic agents that may render her infertile should also be referred to reproductive endocrinologist and infertility specialists to discuss ovarian preservation prior to therapy.

16 Prenatal Care

An often-overlooked effect of preconception counseling is to educate woman about the importance of early prenatal care and more so accurate dating of pregnancy. Accurate dating of a pregnancy improves outcomes and is a public health imperative. As such, an accurately assigned estimated due date (EDD) is among the first evaluations during prenatal care.

Methods for EDD. The American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine make the following recommendations regarding the method for estimating gestational age and due date (2014):

- Ultrasound measurement of the embryo or fetus in the first trimester is the most accurate method to establish or confirm gestational age.
- If pregnancy resulted from ART, the ART-derived gestational age should be used to assign the EDD.

- As soon as data from the last menstrual period (LMP), the first accurate ultrasound examination, or both are obtained, the gestational age and the EDD should be determined, discussed with the patient, and documented clearly in the medical record. Subsequent changes to the EDD should be reserved for rare circumstances, discussed with the patient, and documented clearly in the medical record.
- For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the LMP alone, should be used as the measure for gestational age.

Following the establishment of an accurate EDD, the first prenatal visits involves a discussion of the risks, benefits, and alternatives of various methods of prenatal screening and diagnostic testing, including the option of no testing, which should occur with all patients. Genetic disease screening can suggest increased risk for specific diseases such as muscular dystrophy, fragile X, or Down syndrome, for which genetic counseling should be offered. Information about screening versus diagnostic tests, such as chorionic villus sampling or amniocentesis, can be explained. In some instances, genetic counseling may result in a decision to forego pregnancy or to use ART. In addition to the above, the first prenatal visit includes obtaining baseline prenatal labs: blood type, Rh status, antibody screen, CBC, Rubella, RPR, HBsAg, HIV, urine culture, Pap test, and gonorrhea and chlamydia (if indicated).

Any further discussion about prenatal care is beyond the scope of this chapter.

17 Summary

The goals of preconception care are:

- To identify potential risks to the mother, fetus, and pregnancy.
- To educate the women about these risks, provide option for intervention and management.
- Initiate interventions to provide optimal maternal, fetal and pregnancy outcomes.

Preconception counseling involves interventions that include health promotion and counseling related to reproductive health risks, optimizing the control of medical disorders, and referral, when appropriate. If pregnancy is not desired, then contraceptive options should be discussed. As such, all reproductive-age women should develop a **reproductive health plan**. Evidence supports an association between preconception counseling and positive changes in maternal behavior before pregnancy, particularly with respect to folic acid intake, improved glycemic control, and reduction in alcohol intake and tobacco use.

Resources: Online resources on preconception care:

- Centers for Disease Control and Prevention http://www.cdc.gov/preconception/freematerials-health-edu.html
- March of Dimes http://www.marchofdimes.org/pregnancy/your-checkup-before-pregnancy.aspx
- Perinatal Foundation http://www.perinatalweb.org/index.php?page=shop.product_details&flypage=shop.flypage&product_id=16&category_id=2&option=com_virtuemart&Itemid=280
- American College of Obstetricians and Gynecologists http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Gynecologic_Practice/The_Importance_of_Preconception_Care_in_the_Continuum_of_Womens_Health_Care

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Management of Intraepithelial Lesions of the Cervix

Morgan Elizabeth Fullerton

Contents

Abstract

Cervical cancer is the most common gynecologic malignancy worldwide, with a particularly significant presence in developing nations. In the United States, significant reductions in the rate of cervical cancer have been achieved through improved screening and treatment of precancerous lesions. The screening guidelines have continued to evolve with the most recent guidelines published by the American Society for Colposcopy and Cervical Pathology (ASCCP) in 2012. These guidelines describe the screening process and outline the recommended management for abnormal findings. Screening for cervical cancer consists of cervical cytology and HPV genotyping. The timing and use of these tests depends on the woman's age. If abnormalities are found in screening, the next step is typically colposcopy for directed biopsies. If those biopsies identify cervical intraepithelial neoplasia, treatment may be recommended with excisional procedures or ablation depending on the level of abnormality and age of the patient. Ultimately, the goal of cervical cancer screening is to identify and treat abnormal lesions prior to them progressing to invasive cancer.

Keywords

Cytology • Co-testing • HPV • CIN

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1 Cervical Cancer Screening

Significant reductions have been made in the prevalence of cervical cancer with the advent of cervical cancer screening. Recommendations for the screening for cervical cancer and cervical cancer precursors have evolved over the last decade. In 2012 the American Society for Colposcopy and Cervical Pathology (ASCCP) in conjunction with the American Cancer Society and American Society for Clinical Pathology published updated guidelines on cervical cancer screening. These recommendations changed the initial age of screening, timing of screening, and screening modality for certain age groups. These changes are based on evidence that demonstrates reduced cost with minimal loss in detection of cervical cancer and cervical cancer precursors (Saslow et al. 2012). Current screening guidelines are demonstrated in Table 1.

The precursor to cervical cancer is cervical intraepithelial neoplasia (CIN). The changes in cervical tissue are caused by an infection with the human papillomavirus (HPV). HPV infection is common, especially in women in their teenage years and early twenties. Approximately one third of women between the ages 14 and 24 years old will test positive for HPV (Dunne et al. 2007). Only a small portion of women infected with HPV will have a persistent infection that will lead to cervical abnormalities and put them at risk of invasive cervical cancer. The majority of women will spontaneously resolve their HPV infection within 8 months (Ho et al. 1998). There are also multiple genotypes of HPV, and not all genotypes of HPV are oncogenic. The most oncogenic HPV genotypes are 16 and 18, with HPV-16 being responsible for approximately 55–60 % of cervical cancer cases worldwide. HPV-18 is responsible for approximately 10–15 % of cervical cancer cases, and there are ten remaining genotypes that are responsible for the remainder of cases (de Sanjose et al. 2010; Wheeler et al. 2009). It is over a long period of time with a persistent HPV infection that cervical neoplasia occurs and evolves into cervical cancer.

> The goal of cervical cancer screening is to identify those women with persistent HPV infections that are causing cervical intraepithelial neoplasia and intervene prior to their development of invasive cervical cancer.

Screening for cervical cancer should not begin prior to age 21 years old due to many adolescents being exposed to HPV with typically rapid clearance of the virus. On average this age group will clear HPV in 8 months (Dunne et al. 2007). If HPV caused cervical neoplasia in these affected women, it typically clears with resolution of the infection (Moore et al. 2007; Moscicki et al. 2004). If women in this age group are screened, there would be a higher rate of false positive tests and a greater risk of intervention for lesions that would likely clear on their own and never progress to cervical cancer. The risk of invasive cervical cancer in this age group is very low, and it accounts for 0.1 % of cases (Howlader et al. 2015).

Table 1 Cervical cancer screening guidelines

Age	Screening modality	Time interval
<21 years old	No screening	NA
21–29 years old	Cytology alone	Every 3 years
30–65 years old	Cytology and HPV "co-testing" (preferred)	Every 5 years
	OR	
	Cytology alone (acceptable)	Every 3 years
>65 years old	No screening if meet guidelines	
After hysterectomy	No screening if hysterectomy not done for CIN or cervical cancer	

Adapted from Saslow et al. (2012)

In women age 21–29 years old, screening is recommended to be by cervical cytology only due to a high prevalence of HPV in this age group that has a high clearance rate and a low likelihood of progression to cervical cancer (Dunne et al. 2007; Howlader et al. 2015). The goal of using cytology alone is to reduce the rate of interventions for lesions that would likely clear on their own. This is especially important in reducing the risk of excisional procedures that could lead to cervical insufficiency and preterm birth with women who have a long reproductive life ahead of them. The interval for screening was increased to every 3 years from annual screening with the new guidelines in 2012. This change in frequency reduces the large cost associated with annual screening and interventions with only a slight decrease in the amount of cervical cancer cases prevented (Saslow et al. 2012).

In women age 30–65 years old, recommended screening is cervical cytology with HPV testing, referred to as co-testing, every 5 years (Saslow et al. 2012). If HPV testing is not available, then screening with cervical cytology alone every 3 years is acceptable. The previous recommendation was for annual cytology exams. The change to screening every 3 years with cytology alone allows for a marked decrease in the amount of cytology screening tests and colposcopic examinations with an associated excess risk of cervical cancer of 3 in 100,000 (Sawaya et al. 2003). HPV testing is recommended in this age group because it increases the detection rate of CIN2 and CIN3 (Naucler et al. 2007). Furthermore, positive HPV tests in this age group may represent a persistent infection, and a persistent infection is more likely to progress to high-grade lesions (Kjaer et al. 2010) and cervical cancer (Chen et al. 2011). The addition of HPV testing also increases the detection rate of adenocarcinoma of the cervix (Katki et al. 2011).

Women older than 65 years do not require further cervical cancer screening if they have an adequate negative screening history. An adequate negative screening history requires that they have consecutive negative cervical cancer screening tests within the last decade prior to ceasing screening – this could be either two negative co-tests or three negative cytology screens (Saslow et al. 2012). This is due to the low risk of CIN2 or greater and cervical cancer in this population if adequately screened previously and the duration invasive cervical cancer takes to develop (Saslow et al. 2012). Reasons why cervical cancer screening would be extended past the age of 65 years old is if the patient did not have adequate negative screening previously or had been previously treated for CIN or cervical cancer within the last 20 years.

For women who have been treated for CIN or cervical cancer, they are at risk of recurrence. This risk is highest within the first few years after treatment but persists for longer (Soutter et al. 2006; Melnikow et al. 2009). Current guidelines recommend continued surveillance with age-appropriate screening until 20 years after treatment (Saslow et al. 2012).

Screening should still be performed if a woman is pregnant. Typically, it is performed at her first prenatal visit if she is due for age-appropriate screening. Management may differ based on the findings during further evaluation given her pregnant status, but screening should still be performed (Stonehocker 2013).

There are no clear guidelines on screening for women who are immunocompromised, including those women with HIV or on immunosuppressive therapy. Given their decreased ability to clear infections, they should be screened more frequently (ACOG 2012).

The CDC currently recommends that women diagnosed with HIV should be screened following the diagnosis of HIV and annually thereafter.

Similar to ASCCP guidelines, the CDC recommends screening women with HIV with cytology

only if under the age of 30 years old and cytology only or co-testing with HPV genotyping if 30 years or older. If screening is negative on an annual basis with cytology for three consecutive years, then they can move to screening every 3 years. If co-testing is negative, they can then be screened every 3 years. Screening women with HIV should start within 1 year of the onset of sexual activity, even if this is below the age of 21 years old (Panel on Opportunistic Infections 2015). For women who are immunocompromised in the absence of HIV infection, ACOG has stated that given the lack of data, it is acceptable to perform annual cytology (ACOG 2012). Management of abnormal screening findings should still follow the standard ASCCP guidelines (Massad et al. 2013).

1.1 Cytology

Cervical cytology, or the Papanicolaou test, is the standard mode of cervical cancer screening and requires the smearing of cervical cells from the transition zone onto a slide for interpretation by pathologists. Conventional cytology required the provider to smear the cells onto the slide. Liquid preparation tests are now widely available where the cells are collected by the provider and placed in a preservative liquid that cytotechnologists then process and subsequently prepare the slide. The benefits of liquid preparation are that it is less susceptible to blood, semen, or lubricant affecting the specimen, and the same sample can be used for HPV testing. Neither method has been demonstrated to be more effective in identifying abnormalities (Arbyn et al. 2008; Siebers et al. 2009).

1.2 HPV Testing

There are various HPV tests on the market. When co-testing is performed, it usually is a test to identify if a high-risk HPV genotype is present. Genotypes HPV-16 and HPV-18 are the most commonly seen in invasive cervical cancer, together accounting for 75 % of cases of cervical cancer (de Sanjose et al. 2010; Wheeler et al. 2009). In some cases, management is dependent on the type of HPV genotype present. For example, it is only if HPV-16 or HPV-18 is present that treatment is recommended. There are tests to specifically identify HPV-16 and HPV-18 genotypes in those situations.

2 Abnormal Cytology

The results of cervical cytology are reported according to the Bethesda classification. Within this classification, it is noted if the cytology is normal, reported as negative for intraepithelial lesion (NIL), or abnormal. Abnormal cervical cytology includes the diagnoses of atypical squamous cells, low-grade intraepithelial lesions (LSIL), high-grade intraepithelial lesions (HSIL), atypical glandular cells (AGC), squamous cell carcinoma, endocervical adenocarcinoma in situ (AIS), or adenocarcinoma. The atypical squamous cells can be further divided into the categories of undetermined significance (ASC-US) or cannot exclude HSIL (ASC-H) (Nayar and Wilbur 2015).

When an abnormal cervical cytology result is obtained, it requires follow-up. The ASCCP put forth updated guidelines in 2012 regarding the management of abnormal cervical cytology (Massad et al. 2013).

2.1 ASC-US

For women with ASC-US, reflex HPV testing should be performed on women 25 years and older. If they are HPV negative, then they should undergo repeat co-testing at 3 years. If they are HPV positive, then they should proceed to colposcopy. If no CIN is identified on colposcopy, then repeat co-testing should be performed in 12 months. If the repeat co-testing in 12 months is positive for HPV or cytology is again ASC-US or worse, then colposcopy should be repeated. If that repeat co-testing at 12 months is negative, they can return to age-appropriate screening in 3 years (Massad et al. 2013). In the setting that reflex HPV testing cannot be performed, then repeat cytology should be performed in 1 year, and if negative,

they can return for repeat cytology in 3 years and if ASC-US or worse, then proceed to colposcopy (Massad et al. 2013; Saslow et al. 2012).

In women with ASC-US who are 21–24 years old, repeat cytology in 1 year is recommended. If reflex HPV testing is performed in this population, immediate intervention is not recommended for HPV-positive results. If they are ASC-US/HPV positive, they should have repeat cytology in 12 months. If they are ASC-US/HPV negative, they return to routine screening with cytology in 3 years (Massad et al. 2013).

In postmenopausal women who have an ASC-US-/HPV-negative result in the setting of trying to discontinue routine screening, it is considered abnormal. These women should have repeat screening with at least cytology, if not co-testing, in 1 year (Massad et al. 2013).

In regard to ASC-US/HPV positive, the 5-year cumulative risk of CIN3 is 6.8 %. This is slightly higher than the 5.2 % for LSIL, which is why colposcopy is recommended (Katki et al. 2013a). Typically, HPV genotype is not specifically identified. If HPV-16 or HPV-18 is identified, then the risk of CIN2 or greater is almost doubled (Stoler et al. 2011).

2.2 LSIL

Women with LSIL who are 30 years or older and HPV positive or HPV unknown should proceed to colposcopy. For women who are LSIL and HPV negative, it is preferred to repeat co-testing in 1 year, though proceeding to colposcopy is acceptable. If co-testing in 1 year is abnormal, then they should proceed to colposcopy, even if cytology is only ASC-US. If the co-testing is negative, they should repeat co-testing in 3 years (Massad et al. 2013).

Women who are 21–24 years old should have repeat cytology in 1 year. If that repeat cytology demonstrates ASC-H, AGC, HSIL or worse, then they should undergo colposcopy. If it is negative, ASC-US, or LSIL, then they should have cytology repeated again in 1 year. If that cytology in 1 year, now 2 years from the original LSIL, is persistently abnormal with ASC-US or worse, then they should proceed to colposcopy (Massad et al. 2013). Women in this age group have a lower risk of CIN3 than older women with the same cytology result of LSIL (Katki et al. 2013b).

> Women who are 25–29 years old with LSIL should not have co-testing performed based on age-appropriate screening and therefore should proceed to colposcopy. Even if HPV results are available, they should proceed to colposcopy (ACOG 2013).

Postmenopausal women with LSIL and HPV-positive testing should undergo colposcopy. If there is no HPV result, they have three options: (1) undergo HPV testing, (2) repeat cytology at 6 and 12 months, or (3) undergo colposcopy. If HPV testing is negative, then they should have repeat cytology in 1 year. If they choose to have cytology at 6 month intervals for 1 year and both are negative, they can then return to age-appropriate screening. If either cytology is abnormal, then they should proceed with colposcopy (Massad et al. 2013).

In women who undergo cytology alone that demonstrates LSIL, reflex HPV testing is not generally recommended given 77 % of them will be HPV positive (Arbyn et al. 2006). The recommendation to proceed to colposcopy in the majority of cases of LSIL cytology are because 25 % of these women will have CIN2 or higher on directed biopsies at that time or on close follow-up over the next 2 years (ALTS group 2003).

2.3 ASC-H

Women with ASC-H should proceed to colposcopy regardless of their HPV status (Massad et al. 2013). The risk of CIN2 or greater in women with ASC-H is higher than it is for ASC-US or LSIL but lower than that of HSIL (Katki et al. 2013c). The majority of women with ASC-H are HPV positive; therefore, HPV testing is not recommended to further stratify their risk of CIN

or invasive cervical cancer (Katki et al. 2013d; Massad et al. 2013).

Even women who are 21–24 years old should proceed with colposcopy with ASC-H cytology. They should undergo a diagnostic excisional procedure if colposcopy findings are inadequate or CIN2, CIN3, or ungraded CIN is noted on endocervical sampling. If CIN2 or greater is not identified on colposcopy, they should for followed closely with serial colposcopy and cytology testing at 6 month intervals for up to 2 years with intervention as appropriate. If they have two consecutive negative cytology results and no evidence of high-grade lesions on colposcopy, they can return to routine screening (Massad et al. 2013).

2.4 HSIL

Women with HSIL should undergo colposcopy. If they are 25 years or older, immediate loop electrode excisional procedure (LEEP) is acceptable as well. If colposcopy is inadequate, then a diagnostic excisional procedure should be performed. Around 60 % of women with HSIL will have CIN2 or greater on directed biopsy within the next 2 years (Sherman et al. 2006). Approximately 7 % of women age 30 years old or greater with HSIL will be diagnosed with cervical cancer within the next 5 years (Katki et al. 2013b, d). HPV status with HSIL is irrelevant because there is still an almost 30 % chance of developing CIN3 and 7 % chance of developing cervical cancer in the next 5 years if HPV testing is negative. The rate of HPV positivity is also as high as 94 % in patients with HSIL cytology (Katki et al. 2013d).

Women who are 21–24 years old should undergo colposcopy as well, but immediate LEEP is unacceptable. The management recommendations for this age group are the same as ASC-H (Massad et al. 2013).

2.5 AGC

All women with AGC should undergo colposcopy and endocervical sampling regardless of HPV status. If they are greater than 35 years old or younger than 35 years old with risk factors for endometrial neoplasia, they should undergo endometrial sampling as well. If the cytology notes atypical endometrial cells, then endometrial sampling should be obtained regardless of age, and colposcopy can be either performed at the same time or deferred until endometrial results return and are negative for any abnormality (Massad et al. 2013).

AGC is a rare finding on cytology, reportedly around 0.2 % in 2002 (Davey et al. 2004), and is poorly reproducible (Lee et al. 2002). It can frequently be seen with polyps and reactive changes, though it can also be seen with neoplasia of the cervix, endometrium, ovary, or fallopian tube (Zhao et al. 2009).

If colposcopy is performed and CIN2 or greater is not noted, then repeat co-testing should be performed at 1 and 2 years with plans for colposcopy if any test is abnormal (Massad et al. 2013).

In women with ACG that favors neoplasia or endocervical AIS, a diagnostic excisional procedure is recommended, even if no lesion is identified during colposcopy. The excision should provide an intact specimen with interpretable margins followed by endocervical sampling (Massad et al. 2013); therefore, cold knife cone (CKC) is recommended over loop electrode excisional procedure (LEEP) (ACOG 2013).

2.6 Other

For women with negative cytology and positive HPV testing, they should either undergo repeat co-testing in 1 year with plans for colposcopy if either test is abnormal or proceed with HPV genotyping. If HPV-16 or HPV-18 is identified, then they should proceed with colposcopy. If they are negative for those two HPV genotypes, then they should undergo repeat co-testing in 1 year (Massad et al. 2013). The risk of CIN2 or greater in this population is up to 6 % in women with high-risk HPV and up to 11 % in women with HPV-16 or HPV-18 (Wright et al. 2011). Given that most HPV infections will clear within 12 months, repeat co-testing is recommended. If the HPV infection is persistent, then the risk of

CIN is greater and colposcopy should be performed (Castle et al. 2009).

For women with unsatisfactory cytology and HPV status that is negative or unknown, repeat cytology should be performed in 2–4 months. If HPV positive, they can either proceed to colposcopy or repeat cytology in 2–4 months. If cytology is unsatisfactory twice, then colposcopy should be performed (Massad et al. 2013). Typically, the cytology is unsatisfactory given insufficient squamous cells to reliably detect epithelial abnormalities (Siebers et al. 2012).

For women with negative cytology but absent or insufficient endocervical cells, their management is age dependent. This result suggests that the squamocolumnar junction was not adequately sampled and thus could lead to missed disease. Under the age of 30 years old, they should proceed with routine screening and HPV testing should be avoided. If they are 30 years or older, they should either have HPV testing or undergo repeat cytology in 3 years. If HPV is positive, they should have co-testing in 1 year. If HPV presence is persistent at that time, then they should proceed to colposcopy or they can undergo genotyping at the time, and if HPV-16 or HPV-18 is present, then undergo colposcopy immediately (Massad et al. 2013). Negative cytology despite absent or insufficient endocervical component still provides a good negative predictive value (Elumir-Tanner and Doraty 2011).

Additionally, the results of cervical cytology can also be used for the diagnosis of vaginal infections or identification of atrophy or reactive changes consistent with history of radiation, presence of intrauterine device (IUD), or inflammation. Vaginal infections that can be noted on cervical cytology include bacterial vaginosis, candidiasis, trichomoniasis, and actinomyces (Nayar and Wilbur 2015).

3 Cervical Intraepithelial Neoplasia

When colposcopy is performed, the provider is trying to visually identify abnormal lesions on the cervix with the aid of acetic acid and a colposcope. Directed biopsies under the guidance of colposcopy are the standard for disease detection. Even if lesions are not directly visualized, random biopsy can be used to attempt to identify CIN. Any abnormality should be biopsied regardless of impression (ACOG 2013).

When performing colposcopy, it is important to note if the entire transformation zone is visualized. A colposcopy is considered unsatisfactory if the transformation zone cannot be fully examined. When the entire transformation zone cannot be easily visualized, the provider may use an endocervical speculum or manipulate the cervix in different directions in order to improve exposure. If the colposcopy is unsatisfactory or if a lesion is extending into the cervical canal with ASC-US or LSIL cytology, endocervical sampling should be performed. Additionally, women with ASC-H, HSIL, AGC, or AIS cytology should have endocervical sampling performed either at time of colposcopy if no excision is planned or after excision to assess for any residual disease (Massad et al. 2013).

Depending on the lesion, there are different diagnostic excisional procedures available.

3.1 LEEP

Loop electrode excisional procedure (LEEP) is when cautery with a loop electrode is used to excise the distal portion of the cervix including the transformation zone in an attempt to simultaneously diagnose any further disease and treat it with excision. This procedure can be performed in the office.

3.2 CKC

Cold knife cone (CKC) is similar to a LEEP in that it removes the distal portion of the cervix, but it uses a scalpel instead of cautery. The absence of cautery allows for better interpretable margins for the pathologists, but it leads to an increased amount of bleeding with the procedure. Given the increased bleeding, the procedure is performed in an operating room.

3.3 Cryosurgery

Cryosurgery, also referred to as cryotherapy or ablation, can be an acceptable alternative to excisional procedures in the absence of invasive disease. It is when the cervical dysplasia is treated by freezing the identified abnormal portions of the cervix. Per ASCCP guidelines, ablation is unacceptable if a colposcopy has not been performed or is inadequate or if the endocervical sampling demonstrates CIN2 or higher dysplasia. Additionally, an excisional procedure should be favored over ablation in the setting of a recurrent lesion (Massad et al. 2013). The World Health Organization (WHO) recognizes that access to excisional procedures is not always readily available and recommends cryosurgery over no treatment at all in these situations (WHO 2011).

3.4 No Lesion

If no lesion is found on colposcopy biopsies and the preceding cytology was ASC-US or LSIL, then co-testing in 12 months should be performed. If that co-testing is negative, then they can proceed with age-appropriate screening in 3 years. If the co-testing at 12 months is abnormal, then a colposcopy should be repeated (Massad et al. 2013).

If the preceding Pap was ASC-H or HSIL, then the options are diagnostic excisional procedure or co-testing at 12 and 24 months. Co-testing should only be offered to those women who had an adequate colposcopy with negative endocervical sampling. If any of the co-testing results are abnormal, then repeat colposcopy should be performed. If HSIL is again identified on cytology, then they should proceed with a diagnostic excisional procedure. It is also reasonable to have the pathologist review the cytology and histology and discuss the colposcopic findings to see if the diagnosis should be revised. If the diagnosis is revised, then management should follow the ASCCP guidelines for that pathology (Massad et al. 2013).

In women with high-grade cytology and no lesion identified on colposcopy, other reasons for the high-grade cytology should be considered. These other reasons include (1) the presence of a vaginal lesion as opposed to cervical lesion, (2) the colposcopy was not sensitive enough to identify a lesion with acetic acid alone, or (3) the cytology may have been misread or overread. In order to identify vaginal lesions, a careful colposcopy must be performed with thorough examination of the vagina including the fornices. If no lesions are seen on colposcopy with acetic acid alone and there is a high suspicion for an abnormality, it may be useful to apply Lugol's solution (ACOG 2013). Review of cytology is also reasonable in these cases given up to 50 % of cases will be downgraded to LSIL, ASC-US, or even NIL (Stoler and Schiffman 2001).

If these patients with ASC-H or HSIL and negative colposcopic biopsies do not undergo a diagnostic excisional procedure, then close follow-up is necessary (Massad et al. 2013).

3.5 CIN1

The management of CIN1 in women 25 years and older is similar to that described above for no lesion (Massad et al. 2013). In women who are 21–24 years old, treatment with a diagnostic excisional procedure should be deferred. Instead, it is recommended that they continue with surveillance with cytology and colposcopy. If the preceding cytology was ASC-US or LSIL, then repeat cytology in 12 months is recommended. Colposcopy is recommended if the repeat cytology is ASC-H or HSIL at 12 months or the repeat cytology at 24 months is ASC-US or worse. If they have two negative annual cytology results, they can return to routine screening (Massad et al. 2013). If the preceding cytology was ASC-H or HSIL, then they should be closely followed with colposcopy and cytology every 6 months for up to 24 months as long as the colposcopic exams are adequate and endocervical assessment is negative. Biopsy is recommended for any high-grade lesions or if HSIL is persistent at 1 year. If CIN2 or CIN3 is identified during these exams, then management is per those guidelines. If HSIL is persistent at 24 months without identification of

CIN2 or greater, then a diagnostic excisional procedure is recommended. A diagnostic excisional procedure is also recommended if the colposcopy is inadequate or CIN2 or greater or ungraded CIN is seen on endocervical sampling (Massad et al. 2013).

3.6 CIN2–3

Women with CIN2, CIN3, or CIN2–3 should undergo excision or ablation if colposcopy is adequate. If this is recurrent disease, colposcopy is inadequate, or if endocervical sampling is positive for CIN, they should undergo a diagnostic excisional procedure. Ablation would be considered inappropriate (Massad et al. 2013). Treatment is recommended in these women given CIN3 is a cervical cancer precursor (Östör 1993).

Women desiring future fertility who believe the risk of pregnancy complications, including preterm delivery, from treatment of their cervical lesions outweighs their risk of developing cervical cancer during observation can undergo observation instead of treatment. Observation would include colposcopy and cytology at 6 month intervals for 12 months. In young women with CIN2, observation is preferred, but treatment is acceptable. In women with CIN3 or inadequate colposcopy, treatment is preferred (Massad et al. 2013) given the increased risk of cervical cancer in the future if left untreated (Östör 1993). It is more acceptable for CIN2 to undergo observation given it has a higher rate of regression than CIN3 and low rate of progression to cancer in the short term (Östör 1993). If CIN2 or CIN3 are persistent for 2 years, then treatment with a diagnostic excisional procedure is recommended (Massad et al. 2013).

After treatment for CIN2 or CIN3, co-testing should be performed at 12 months and 24 months. If both are negative, then co-testing should be repeated in 3 years, and if again negative, they can return to routine screening for at least 20 years. If any of the test results are abnormal, then colposcopy with endocervical sampling should be performed (Massad et al. 2013). Most recurrent or persistent CIN will be identified within the first 2 years of treatment, but there is persistent increased risk of invasion for at least 10 years, and cancer can be found as delayed as 20 years after treatment (Hellberg et al. 1994; Soutter et al. 2006).

3.7 AIS

The treatment of AIS depends on the woman's desire for future fertility. If she has completed childbearing and AIS is noted on a diagnostic excisional procedure, then she should have a hysterectomy. If she still desires future fertility, then conservative management can be pursued. If her prior excisional procedure has negative margins, then she should undergo co-testing, colposcopy, and endocervical sampling in 6 months. If the margins are involved or endocervical sampling is positive for CIN or AIS, then she should undergo another excisional procedure to completely remove the lesion (Massad et al. 2013). Even if negative margins are obtained, there is still an approximate 11 % persistent risk of AIS and a small risk of invasive cancer (Costales et al. 2013).

3.8 Special Populations

3.8.1 Young Women

Young women are those who consider the risks of treatment of their cervical lesion outweigh the risks of an excisional procedure on their future fertility. There is no age limit on this group (Massad et al. 2013). They are typically managed more conservatively with serial observation, rather than treatment, unless they have CIN3. Given the risk of cervical cancer with CIN3, treatment in this case is recommended (Massad et al. 2013; Östör 1993).

3.8.2 HIV/Immunocompromised

Per ACOG, women with HIV who have been diagnosed with CIN2 or CIN3 should have more vigilant surveillance after treatment. Instead of having co-testing at 3 years after two annual negative co-tests, they should undergo

co-testing on an annual basis. This is due to their increased risk of recurrent disease given their immunocompromised status which makes it difficult for them to clear HPV. This is also true for women who are on immunosuppressive therapy (ACOG 2013). The CDC guidelines regarding management and surveillance of CIN in patients with HIV do not specifically designate different time frames than what is recommended by the ASCCP (Panel on Opportunistic Infections 2015).

3.8.3 Pregnant

Women who are pregnant with abnormal cervical cancer screening results will typically undergo conservative management given the increased risk of bleeding, potential for fetal loss, and risk of preterm delivery with intervention (ACOG 2013). The goal of screening during pregnancy is to identify cervical cancer (Massad et al. 2013). Biopsy is typically limited to those lesions concerning for CIN2, CIN3, or cancer, though biopsy of any lesion is acceptable and has not been reported to cause fetal loss of preterm delivery. Risk of fetal loss and preterm delivery are increased with a diagnostic excisional procedure. Endocervical sampling is never recommended given its risk for cervical laceration or disruption of the amniotic membranes. Colposcopy during pregnancy is a challenge due to increased vascularity and mucous as well as the development of epithelial changes that can mimic CIN. Redundant tissue can also make it difficult to visualize the cervix (ACOG 2013).

For ASC-US cytology, colposcopy is recommended but can be deferred until 6 weeks postpartum. If colposcopy is performed during the pregnancy, they should still have postpartum follow-up. For LSIL cytology, colposcopy is preferred, but it can also be deferred until 6 weeks postpartum (Massad et al. 2013). All women with HSIL should undergo colposcopy with the goal to identify invasive cervical cancer (Massad et al. 2013; ACOG 2013). If there is no evidence of invasive cervical cancer, then any treatment intervention should be deferred until postpartum. If CIN1 is identified, then they should follow-up without treatment. If CIN2 or CIN3 is identified, then serial colposcopy exams can be performed during the pregnancy, though no sooner than every 12 weeks. Repeat biopsy would be recommended only if the lesion worsens or the cytology is suggestive of invasive cancer. Deferring reevaluation until 6 weeks postpartum is acceptable given the low risk of rapid progression to invasive cancer over the duration of a pregnancy (Massad et al. 2013). Invasive cervical cancer is the only reason why treatment would be recommended during pregnancy, and that would include a discussion on altering the route and timing of delivery. CIN2 and greater may also resolve in the immediate postpartum period, which is why repeat colposcopy with cytology is deferred until at least 6 weeks postpartum (Massad et al. 2013; Stonehocker 2013).

4 Conclusion

Cervical cancer screening is an integral part of women's health. The ASCCP has put forth guidelines regarding the timing of screening as well as recommendations on how to proceed with abnormal findings. These recommendations will continue to evolve as further research clarifies the role of HPV testing in screening and the natural course of cervical intraepithelial neoplasia is better understood. In general, women with persistent high-risk HPV should undergo more aggressive surveillance for precancerous lesions of the cervix, and women with CIN2 or CIN3 on colposcopic guided biopsy should undergo excisional procedures for both definitive diagnosis and potential treatment of precancerous lesions. Women who are immunocompromised warrant more active surveillance. Women who are desiring future fertility should have those considerations taken into account when being counseled regarding more invasive procedures that could lead to greater risks with their future pregnancies. While clear guidelines exist for the screening for and management of abnormal cervical lesions, further advancements are anticipated as research continues in this field.

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Impact of Obesity on Gynecological Diseases

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Abstract

Obesity is a chronic illness affecting more than one-third of adults in the United States. In addition to being associated with some of the leading causes of death such as diabetes, heart disease, and stroke, obesity also profoundly affects women's gynecologic health by altering the reproductive cycle thus affecting menstruation, procreation, and contraception, among others. The rate of certain malignancies is also increased. This chapter reviews the impact of obesity on gynecologic aspect of women's health.

Keywords

Obesity • Puberty • Contraception • Infertility • Anovulation • Surgery • Gynecology

1 Introduction

Obesity is an epidemic affecting more than one-third of all adults in the United States. The Centers for Disease Control and Prevention (CDC) reports that 17 million children and 78.6 million adults are affected in the United States, with an estimated annual medical cost for obesity in the United States of $147 billion in 2008. Obesity is the most prevalent among middle-aged adults, with different groups being affected differently; non-Hispanic Blacks have the highest age-adjusted rates (47.8%), followed by Hispanics (42.5%), non-Hispanic Whites (32.6%), and non-Hispanic Asians (10.8%) (Centers for Disease Control and Prevention 2015).

The body mass index (BMI) is a measurement obtained by dividing the person's weight (in kilograms) by the square of the person's height (in meters squared). The parameters for the definition of overweight and obesity vary by race. In some populations, health risks are seen at a much lower BMI (South Asians) and in others at a higher BMI (Blacks) when compared with Caucasians. The classifications for BMI adopted by the National Institute of Health (NIH) and World Health Organization (WHO) for Caucasian, Hispanic, and Black individuals are summarized in Table 1; a normal BMI is between 18.5 and 24.9 kg/m^2, overweight is BMI $\geq$25 kg/m^2, and obese is a BMI $\geq$30 kg/m^2. These cutoffs would underestimate the health risk in the Asian and South Asian population. Thus, in the WHO and NIH guidelines for Asians, overweight corresponds to a BMI between 23 and 24.9 kg/m^2 and obesity a BMI >25 kg/m^2.

Table 1 BMI classification in Western countries

Underweight – BMI <18.5 kg/m^2
Normal weight – BMI $\geq$18.5–24.9 kg/m^2
Overweight – BMI $\geq$25.0–29.9 kg/m^2
Obesity – BMI $\geq$30 kg/m^2
Obesity class I – BMI of 30.0–34.9 kg/m^2
Obesity class II – BMI of 35.0–39.9 kg/m^2
Obesity class III – BMI $\geq$40 kg/m^2

In addition to BMI, measurement of waist circumference is vital in recognizing adults at greater health risk, particularly in the individuals whose BMI ranges from 25 to 35 kg/m^2. A waist circumference of $\geq$88 cm in women and $\geq$102 cm in men is considered elevated and suggestive of increased cardiovascular risk. In Asian men and women, a waist circumference >90 cm and >80 cm, respectively, is considered abnormal. In patients with a BMI >35 kg/m^2, measuring waist circumference is unnecessary since these individuals are already at high risk.

Obese individuals are at increased risk of all-cause mortality, in addition to many serious illnesses including hypertension, dyslipidemia, type 2 diabetes, coronary artery disease, stroke, some types of cancer, sleep apnea, osteoarthritis, and mental disorders such as depression and anxiety.

Obese women have a separate set of complications from men resulting from their elevated BMI. The effect of obesity on women's gynecologic health is reviewed in this chapter.

2 Obesity and the Menstrual Cycle

2.1 Puberty

Increases in weight and body fat are associated with a higher likelihood of early menarche. The decreasing age of puberty in the United States is thought to be due to, at least in part, the increasing prevalence of childhood obesity. According to the CDC, data collected over the past 30 years suggest that obesity rates have doubled in children and quadrupled in adolescents. Meanwhile, the overall age of puberty has decreased from approximately 12.75 years in the 1960s to approximately 12.5 years in the 1990s.

Frisch and Revelle (1971) proposed a "critical fat hypothesis", suggesting that puberty is initiated after a threshold level of fat is established (Frisch and McArthur 1974). The link between puberty and fat appears to be a protein hormone named leptin (Ahima et al. 1996). Leptin is produced in adipose tissue, circulates to the brain, and plays a crucial role in controlling hunger. Levels of leptin increase with increasing adiposity. Although a threshold level is necessary for the onset of puberty in females, evidence supports that leptin plays a permissive role. Leptin stimulates Kiss 1 neurons causing the Kiss 1 neurons to transmit metabolic information to GnRH neurons. Some studies have indicated that leptin also has direct gonadal effects that may contribute to the accelerated puberty in obese adolescents (Sanchez-Garrido and Tena-Sempere 2013).

- Leptin-deficient mice fail to develop puberty, and injection of leptin in prepubertal mice triggers puberty.
- Data derived from observation of children with untreated leptin deficiency or leptin receptor deficiency has demonstrated hypogonadotropic hypogonadism and failure to initiate puberty. Hence, leptin may be the link that determines a critical level of fat and allows/triggers the onset of puberty by communicating with higher centers that control the hypothalamic pulses that trigger puberty.
- It has been reported that girls with an early onset of puberty have an increased risk of PCOS and cardiovascular events later in life.

2.2 PCOS and Insulin Resistance

Notoriously associated with insulin resistance, polycystic ovary syndrome (PCOS) is a complex functional endocrine disorder with clinical features of chronic anovulation, hyperandrogenism, and a derangement in follicular development resulting in polycystic-appearing ovaries. Women with PCOS have a unique disorder of insulin action resulting in a significant insulin resistance that is independent of obesity (Dunaif et al. 1989). The combination of PCOS and obesity has synergistic adverse effects glucose tolerance (Dunaif et al. 1989).

Obesity is characterized by insulin resistance. With increasing weight, the levels of circulating insulin increase, causing a downregulation and decrease in the number of insulin receptors coupled with a concomitant increase in insulin resistance. In insulin resistance, fat, muscle, and liver cells are unable to respond normally to circulating insulin, and thus, higher levels of insulin are needed to help glucose enter the cells. The metabolism of proteins, carbohydrates, and fat and the catabolism of triglycerides are affected by high levels of glucose, leading to an increase in the levels of circulating free fatty acids and LDL cholesterol. The hyperinsulinemia associated with obesity is reversible with weight loss.

Obesity contributes to chronic anovulation in several ways. First, the previously described hyperinsulinemia stimulates androgen production in the ovarian stroma, impairing follicular development. Also, with increasing adipose tissue, peripheral aromatization of androgens results in increased levels of estrogen that exert a negative feedback on the hypothalamo-pituitary-ovarian axis. Furthermore, levels of sex hormone-binding globulin (SHBG), a protein carrier produced in the liver that transports the principal sex steroids, are inversely related to body weight. In obese women, low levels of hepatic SHBG lead to further

increases in unbound levels of testosterone and estradiol in the circulation.

The chronic anovulation associated with obesity results in a state of unopposed estrogen that drives the proliferation of endometrial tissue and the resultant frequent, irregular bleeding. Studies have suggested that more than a third of overweight and obese women have irregular menses and that menstrual irregularity correlates with increasing BMI (Hedley et al. 2004). The effect of unopposed estrogen on the endometrium can also result in endometrial hyperplasia and cancer (discussed below, Sect. 7).

Weight loss alone can restore ovulation in patients with PCOS. A moderate decrease in body weight of 5–10% has been shown to be associated with a return of ovulatory function in the majority of obese anovulatory women with PCOS (Crosignani et al. 2003).

The state of hyperestrogenism associated with obesity has also been implicated in the pathogenesis of endometrial polyps. A study by Onalan et al. (2009) demonstrated that obesity was an independent factor in the development of endometrial polyps and positively correlated with their size and number, which could be another factor manifesting with abnormal uterine bleeding in obese women.

3 Infertility and ART

While many obese patients are not infertile, obesity was found to be associated with decreased fertility, diminished response to infertility treatments, and increased risk of miscarriage.

3.1 Fertility

A cohort study of 53,910 couples enrolled in the Danish National Birth Cohort found a dose-response relationship between increasing BMI and decreased fecundity (Ramlau-Hansen et al. 2007). As described above (Sect. 2.2), obesity is associated with an endocrinopathy that manifests by hyperinsulinemia and insulin resistance, coupled with hyperandrogenemia, leptin deficiency, increased LH, abnormal FSH-LH ratio, decreased sex hormone-binding globulin, increased estrogen, and decreased progesterone levels. This hormonal profile affects neuroregulation of the hypothalamic-pituitary-gonadal axis resulting in anovulation and decreased fertility. Weight loss is capable of correcting the anovulation associated with obesity and PCOS. Insulin-sensitizing drugs, predominantly metformin, have also been shown to restore ovulation in some women with PCOS.

Beyond anovulation, obesity itself appears to be associated with a lower fecundity (Gesink Law et al. 2007). In a cohort study by Zaadstra et al. (1993), an increased waist to-hip ratio was found to be associated with delay in time to conception, even after adjustment for patient weight and cycle length or regularity. A Dutch study found that the probability of natural conception declined by 4% per kg/m^2 in women with a BMI >29 kg/m^2 (van der Steeg et al. 2008). The mechanisms related to this decrease in fertility in obese ovulatory women are not completely understood.

3.2 Miscarriage

There is evidence that obesity increases the rate of spontaneous abortions by almost threefold compared to women of normal weight. In a retrospective study of 712 egg donation cycles (Bellver et al. 2007), showed the rate of miscarriages to be 13.3% in normal-weight women, 15.5% in overweight women, and 38.1% in obese women. Various theories have been proposed to explain this increased rate. Obesity and the associated endocrine alterations may affect corpus luteum function (Sherman and Korenman 1974; Fedorcsák et al. 2000), early embryo development (Kawamura et al. 2002; Fedorcsák and Storeng 2003), or endometrial receptivity (Alfer et al. 2000; Gonzalez et al. 2000) hence affecting embryo implantation and early development.

3.3 Assisted Reproductive Technology (ART)

In addition to affecting the chances of spontaneous pregnancy, obesity also diminishes success rates with ART. With increasing BMI, there is evidence for an increase in in-vitro fertilization (IVF) cycle cancelation states, increasing gonadotropin requirements, a decrease in the number of oocytes collected, and an overall decrease in the rate of live births. An increase in body habitus also makes the procedure of oocyte retrieval technically challenging with increased rate of complications. At this point in time, many fertility practices will counsel their morbidly obese patients about weight loss prior to initiating ART aiming at a threshold BMI of less than 40 to qualify for IVF.

4 Contraception

4.1 Combination Oral, Transdermal, and Vaginal Contraceptives

Obesity may impair the efficacy of combined contraceptives. There is evidence of a higher risk of oral contraceptive (OC) failure in obese women when compared to normal-weight women. In a study by Holt et al. (2005), it was shown that women with a BMI >27.3 had a 60% higher risk of OC failure and those with a BMI >32.2 had a 70% higher risk. Similar results were seen in clinical trials of the combination transdermal patch, showing increased failure in women weighing above 90 kg (Zieman et al. 2002).

Also, combination OC (COC) and obesity are both independent risk factors for venous thromboembolism (VTE). A case-control study found that in women using oral contraceptives with a BMI greater than 25, the rate of VTE is tenfold higher than in lean women not using oral contraceptives (Abdollahi et al. 2003).

While the American Congress of Obstetricians and Gynecologists (ACOG) (American College of Obstetrics and Gynecology 2006) does not label obesity an absolute contraindication for combined contraceptives, it states OCs should be used with caution in obese women above the age of 35. The CDC Medical Eligibility Criteria [USMEC] rate obesity with BMI $\geq$30 kg/m^2 at category 2 [benefits generally outweigh the risks]; they also say the obese women who use COCs are more likely than obese women who do not use the pill to develop a VTE.

- USMEC puts malabsorptive bariatric surgery into category 3 (risks generally outweigh benefits) although restrictive bariatric procedures [sleeves or bands] are category 2.
- Obese women with hypertension or previous DVT/PE would fall into category 3/4 based on these factors.

Accordingly, consideration should be given to a progestin-only contraceptive or to intrauterine devices. The levonorgestrel intrauterine device is a particularly attractive option for obese women given its non-contraceptive benefits of endometrial cancer risk reduction and decreased menstrual bleeding.

4.2 Progestin-Only Contraceptives

Progestin-only pills (POPs) are not as widely used as COC. They are particularly a good option for postpartum women, where the risk of thrombosis is elevated, since they do not increase the risk of VTE and do not negatively affect breast milk. Despite their increased safety profile, POPs used in the United States are associated with undesirable side effects such as irregular bleeding, and they have a very stringent daily timing (within 3 hours). POPs do not reliably suppress ovulation; however, their effectiveness relies on the changes they exert on the cervical mucus and the endometrium. For obese women, and women with other contraindications to COCs, the POPs offer the advantage that they do not increase the risk of venous thromboembolism while they maintain a success rate similar to that of OC.

Injectable progestins have mechanisms of action similar to POPs that include increased cervical mucus viscosity, creation of an endometrium

unfavorable for implantation, and unpredictable ovulation suppression. Their use is very popular in the United States. Depot medroxyprogesterone acetate (DMPA) has a contraceptive efficacy equivalent or better than that of COC but has a much better safety profile. In obese women, DMPA is safe. There are studies showing possible weight gain with the use of DMPA; however, not all studies have shown this effect.

4.3 Intrauterine Devices (IUD)

IUDs are one of the most effective methods of contraception. There are currently five different IUDs available in the United States, and they include one copper containing IUD and four different levonorgestrel-releasing IUDs. The effectiveness of IUDs is not affected by BMI as the mechanism of action does not rely on systemic hormone levels. In the Contraceptive CHOICE project, the overall failure rates of IUDs were less than one per hundred woman-years with no differences between various BMIs (Xu et al. 2012).

The levonorgestrel-releasing IUD is a particularly attractive option for obese women. It exerts its contraceptive function by rendering the endometrium atrophic and stimulating thick cervical mucus, but its non-contraceptive uses are equally attractive. Since obese women have high rates of dysfunctional uterine bleeding and endometrial hyperplasia (Sect. 2.2), the levonorgestrel-releasing IUD is often used in obese women to minimize vaginal bleeding and decrease the risk of premalignant endometrial lesions.

5 Surgical Risk

Obese women are at higher risk of experiencing surgical and anesthetic complications. In a paradox referred to as the "obesity paradox" (Mullen et al. 2009), otherwise healthy obese patients undergoing non-bariatric surgery were found to have lower mortality and morbidity than normal-weight patients. However, obese patients commonly have comorbid conditions such as hypertension, obstructive sleep apnea, coronary artery disease, or a difficult airway, and these patients have an increased rate of surgical mortality and morbidity compared to the normal-weight patients.

5.1 Surgery in the Obese Patient

Physical exam and particularly the bimanual exam may be difficult in the clinic setting to decide on the preferred route of surgery. In this case, further imaging such as MRI is recommended for guidance. As in all patients, the least invasive route should be considered for better outcomes.

Abdominal surgery in obese women takes longer and has a higher blood loss and higher rate of wound complications and surgical site infections, increased risk of VTE, and increased hospital stay. As the BMI rises, so do the risk of surgical site infection (Olsen et al. 2009) and wound complications (Nugent et al. 2011). Some intraoperative considerations have been suggested for surgery in obese patients. First, placement of the skin incision needs to be tailored to each patient, as anatomy of the abdominal wall may be distorted. In cases where an abdominal fat pad covers the lower abdomen, one must be aware that an incision under the fat pad is subjected to an intense maceration. Also, surgical instruments must be adapted to the situation, using wide retractors to maintain the thick abdominal wall. Mass closure, subcutaneous drains, and prophylactic antibiotics can be considered in order to minimize wound disruption.

The implications for laparoscopic surgery are also present. The position of the umbilicus relative to the aortic bifurcation and the rest of the abdomen vary and may make abdomen penetration with a Veress needle challenging. Open laparoscopic entry has been found to be safer in obese subjects (Byron et al. 1989). Also of concern is that operating in the pelvis requires the patient to be in the Trendelenburg position. This positioning is known to increase intrathoracic pressure and particularly for obese patient may be associated with impaired oxygenation and difficulty in

ventilation. The use of longer trocars and instruments needs to be anticipated. Laparoscopic surgery in obese patients may be more complicated and the risk of conversion to laparotomy is elevated, but these obstacles can be partly overcome with surgical experience (Wattiez et al. 2002).

As with all patients, efforts to choose the least invasive surgery should be exerted. If appropriate, the vaginal route for hysterectomy is preferred to reduce postoperative pain and morbidity. This technique can also be challenging because of the size of the obese patient's legs and buttocks, as well as the presence of redundant vaginal sidewalls, all of which can make visualization and surgery more difficult.

According to the American College of Chest Physicians, obese woman who undergo gynecologic surgery for longer than 45 min fall in the category of moderate risk of VTE and should receive some form of prophylaxis unless at high risk of major bleeding. VTE prophylaxis can either be low molecular weight heparin, low-dose unfractionated heparin, or mechanical prophylaxis with intermittent pneumatic compression.

Appropriately positioning the obese patient is of paramount importance and can prove to be challenging. The operating table can usually accommodate a patient weighing up to 205 kg, and some tables can accommodate up to 455 kg. Positioning of the patient should take into account surgeon ergonomics and provide protection to the patient from nerve injury and pressure sores. If the patient is to be placed in the lithotomy position, the boot-type stirrups are preferred for better lower extremity alignment and decreased pressure on the knees and hips as compared to the candy cane stirrups.

5.2 Anesthesia in the Obese Patient

Risks of anesthesia are higher in obese women with most issues related to technical problems such as constructing an airway, gaining venous access, or providing effective ventilation. Before undertaking gynecologic surgery, a preoperative consultation with an anesthesiologist should be considered. The obese patient has an increase in cardiac output and a relatively lesser increase in blood volume, resulting in a relative hypovolemia with poor tolerance to fluid overloading and hemorrhage. Respiratory function is altered as well. There is a decrease in functional residual capacity and reserve expiratory volume, associated with an increase in the closure capacity and alveolar dead space. This results in a mismatch of ventilation and perfusion that can lead to hypoxia. The oral airway in the obese patient is suboptimal due to decreased neck mobility and narrowing of the pharyngeal space soft tissue effect. In addition, there is an increased risk of aspiration of gastric contents due to the higher intra-abdominal pressure. All of these concerns must be addressed at the preoperative consultation.

6 Urinary Incontinence

Urinary incontinence, a loss of bladder control, affects more than 13 million women in the United States. The four main types of urinary incontinency include stress urinary incontinence (SUI), urge incontinence, overflow incontinence and functional incontinence. Patients often present with mixed symptoms.

Obesity is an independent risk factor for the development of both stress and urge incontinence, with obese women having up to a 4.2-fold greater risk of than women of normal weight (Alling Moller et al. 2000). The severity of incontinence appears to be influenced by the duration and extent of obesity; which could be explained by the raised intra-abdominal pressure caused by central obesity conveying additional pressure on the pelvis and bladder. This association is further corroborated by studies showing that weight loss among obese women leads to a reduction in episodes of urinary incontinence (Subak et al. 2009).

The mid-urethral sling procedure for the management of SUI has been found to be safe and effective in both obese and nonobese women, regardless of BMI (Weltz et al. 2015).

7 Endometrial Cancer and Other Malignancies

Obesity is directly associated with a number of malignancies including colon cancer, kidney cancer, esophageal cancer, as well as endometrial cancer and postmenopausal breast cancer (Bianchini et al. 2002). The normal balance between cell proliferation and apoptosis in vulnerable tissues may be distorted by the endocrinopathies of obesity that includes fat cell alterations in the metabolism of sex steroids, insulin, and growth factors.

Obese women are at a two-fourfold higher chance of developing endometrial cancer than women of normal weight. In obese women presenting for bariatric surgery, the rate of endometrial hyperplasia was found to be 10% (Modesitt et al. 2015).

There are two types of endometrial cancer. Type I endometrioid adenocarcinomas are the most common, comprising 75% of all cases. They are estrogen-dependent and low-grade and are preceded by endometrial hyperplasia. On the other hand, type II endometrial cancers have a serous or clear cell histology and no precursor lesion and are generally more aggressive. Type I is the endometrial cancer that is more common in obese women; since obesity is often associated with hyperestrogenism due to peripheral aromatization of androgens to estrogen in the adipose tissue. More importantly, the chronic anovulatory status, which is frequently seen in obese women, results in the endometrium being exposed to unopposed estrogen. In the absence of progesterone-induced endometrial shedding, endometrial hyperplasia can frequently develop.

While at this time performing an endometrial biopsy for all women with a BMI >30 is not recommended, ACOG recommends sampling the endometrium of all obese women with symptoms of heavy or irregular uterine bleeding regardless of age (ACOG 2012).

Almost half of women with endometrial cancer or hyperplasia don't know that obesity affects their cancer risk (Beavis et al. 2015), so it is the role of providers to identify these patients at high risk and provide them with the appropriate counseling and education.

8 Pelvic Imaging in the Obese Patient

8.1 Ultrasound

Ultrasound is often the imaging modality of choice in gynecology. However, transabdominal ultrasound is the radiologic modality that is the most affected by obesity because of the attenuation of the ultrasound beam by the layers of adipose tissue. Nonetheless, the availability of transvaginal imaging provides easier accessibility to the reproductive organs by bypassing the abdominal pannus. An often-used solution to the decreased penetration of the transvaginal ultrasound is by placing a hand on the pelvic organs to push them closer to the probe, which in some cases may afford better visualization.

Abdominal scanning in the obese patient is often more challenging. The abdominal pannus limits visualization by both increasing the depth of insonation required and by attenuating the strength of the ultrasound beam. The abdominal pannus also increases the ergonomic challenge for the sonographer. Since the pannus is usually at its thickest between the pubis symphysis and the umbilicus, the patient or an assistant can be enlisted for help by lifting the fat pad upwards toward the patient's head, thus providing a flatter and thinner abdominal wall and closer distance to the pelvic organs.

The use of technology such as harmonic imaging, a nonlinear propagation of ultrasound through body tissues, can improve the quality of the image because fat will act to increase the harmonic waves created. Also, when available, the use of the preset "penetration" mode may result in higher quality image.

When ultrasound imaging fails to provide adequate visualization of the pelvic organs, the imaging modality of choice is MRI when a gynecologic condition is suspected. CT scan is preferred in urologic and gastrointestinal conditions.

8.2 Computed Tomography (CT)

CT imaging of the pelvis is generally adequate in obese patients. The main limiting factors for CT imaging in obesity are size of the patient relative to the machine, positioning, artifacts, and radiation exposure. In fact, CT scan manufacturers set a weight limit for the table beyond which the table can be damaged and the warranty is void. Also, the aperture through which the patient should go is set at a diameter of 70 cm, with newer enhanced models fitting up to an 80–90 cm diameter. The best practice in the case of patients with severe obesity is to obtain an exact weight and abdominal girth immediately prior to the procedure. In cases where the abdominal girth may be over the limit, there are abdominal binders that can be used for this purpose, also serving the additional benefit of preventing the pannus from hanging asymmetrically to the side causing artifacts. Another consideration in the use of CT scan is the quantity of contrast material used. The dose is typically obtained by considering the patient's weight, and this may expose obese patients to a higher-than-necessary dose of contrast. A solution to this problem may be to use the lean body weight as opposed to the actual weight.

8.3 Magnetic Resonance Imaging (MRI)

Compared with ionizing radiation or sound waves, the radiofrequency used by MRI penetrates large amount of fat. Hence, MRI is the modality least affected by obesity. Challenges for MRI, like for CT scan, are mostly related to the size of the patient and the problems with positioning and length of the procedure. The tight fit of the patient in the aperture can cause claustrophobia and even motion artifacts. Also, there is a risk of skin burn if the patient is tightly fitting in the gantry. This can be minimized by placing cloth protections at the areas of friction (Glanc et al. 2012).

9 Weight Loss

More than two-thirds of adults in the United States are either attempting to lose weight or preserve their weight. For patients who are overweight or obese and at risk for obesity-associated disorders, a number of weight loss interventions are available, including lifestyle, diet, exercise, pharmacotherapy, and surgery. Even moderate weight loss of 5–10% is associated with a reduction in obesity-associated morbidity.

The role of the physician is to identify patients who would benefit from losing weight, determining an ideal body weight, and educating the patient about available options. The initial management is a combination of diet, exercise, and lifestyle modifications with a goal to create an energy deficit by either decreasing intake or increasing expenditure or ideally both. Pharmacological agents can be a useful adjunct to diet and exercise, with bariatric surgery increasingly used as a final option.

9.1 Diet

In a normal adult, approximately 22 calories are required to maintain a kilogram of body weight. Once a patient's daily energy expenditure is calculated, one can calculate their daily caloric intake that generates a daily deficit. This is also used to estimate the resulting weekly weight loss. Diets providing less than 800 calories per day are not generally recommended.

Balanced low calorie/portion-controlled diets are the most commonly recommended diets. They encourage the intake of foods with adequate nutrients, in addition to proteins, minimal carbohydrates, and essential fatty acids, while eliminating alcohol, sugar-containing beverages, and other sources of food that are high in carbs/calories but poor in nutrients.

- Low and very low carbohydrate diets have been popular for many years. Low carbohydrate diets contain 60–130 g of carbohydrates and very low carbohydrate diets contain up to

59 g of diets. They are based on the fact that restriction of carbohydrates leads to glycogen mobilization and rapid weight loss primarily due to glycogen breakdown. Hence, they are more effective for short-term weight loss than low-fat diets.

- Low-fat diets are another commonly used strategy for weight loss, recommending a reduction in the daily intake of fat to less than 30% of total dietary intake. Considering a diet of approximately 1500 calories, this would mean about 45 g or less of fat, which can be counted using the nutrition information labels on food packages.
- The Mediterranean diet is inspired from the traditional diets of Greece, Spain, and the south of Italy. It includes primarily plant-based foods, such as vegetables, fruits, whole grains, legumes, and nuts. It replaces butter with monounsaturated fats such as olive oil and contains a moderate amount of dairy products and low amount of meat. A meta-analysis of eight cohort studies demonstrated that patients that adhered to a Mediterranean diet had a significantly improved health status, with a reduction in overall mortality, mortality from cardiovascular diseases, incidence and decreased mortality from cancer, and incidence of Parkinson's disease and Alzheimer disease (Sofi et al. 2008).

9.2 Exercise

Exercise alone, without dietary changes, results in only modest reductions or no loss in weight. Adding exercise to diet has only slight additional benefits than diet alone. In a systematic review of 17 randomized trials, it was found that there was only a slight increase in weight loss in the diet and exercise group compared to the diet alone group and that this difference was statistically significant in only two of the studies (Catenacci and Wyatt 2007). However, adding exercise to diet has other important benefits independent of weight loss, such as attenuating the diet-induced loss of muscle mass.

9.3 Pharmacotherapy

In addition to diet, exercise, and lifestyle modification, drug therapy can be a helpful adjunct to weight loss in overweight patients with comorbidities and obese patients. The role of medications for weight loss has been questioned because of concerns about efficacy and safety; hence, the decision to initiate medications should only be made after a thorough evaluation of risks and benefits.

There are five drugs currently approved for long-term use: orlistat, lorcaserin, phentermine-topiramate, bupropion-naltrexone, and liraglutide. Phentermine, benzphetamine, phendimetrazine, and diethylpropion have only been approved for short-term use.

- Orlistat alters fat digestion by inhibiting pancreatic lipases, resulting in incomplete hydrolysis of fat and increased fat excretion in feces. The efficacy of orlistat has been demonstrated in many clinical trials demonstrating that initial weight loss is greater and that weight regain is slowed as compared with lifestyle/placebo. In addition, orlistat showed other beneficial effects such a reduction in HbA1c, improvement in blood pressure, and an improvement in lipid values more than what can be explained by weight loss alone. The predominant side effects are gastrointestinal, mainly cramps, flatus, fecal incontinence, and oily spotting. These side effects are high initially and then subside as patients learn to avoid them by avoiding high-fat diets. Absorption of fat-soluble vitamins (A, D, E, K) is lowered by orlistat therapy.
- Lorcaserin is a selective agonist of the serotonin 2C receptor; it reduces appetite and therefore body weight. It appears to have similar efficacy as and fewer side effects than orlistat. In addition to weight loss, lorcaserin has other beneficial effects including decreases in blood pressure, lipid levels, fasting glucose, and insulin levels. Side effects are generally mild, and they include headache, upper respiratory infections, dizziness, and nausea.

- Liraglutide is a long-acting glucagon-like peptide-1 analog that is available for use in the United States for treatment of type 2 diabetes. It is also approved for use at higher doses in the treatment of obese patients or patients with a BMI $\geq$27 kg/m^2 with at least one weight-related comorbidity. Liraglutide has been associated with a significant reduction in weight when compared to placebo in diabetes and non-diabetes trials. At the higher doses used for obesity treatment, liraglutide has higher rates of nausea and vomiting, side effects that may be partly responsible for the weight loss effect of the drug. Other side effects include diarrhea, hypoglycemia, and anorexia.
- A preparation of combined phentermine and extended-release topiramate has been approved for obese adults or adults with BMI $\geq$27 kg/m^2 with at least one weight-related comorbidity. This combination has been shown to increase weight loss in the first year of use. The most common side effect is dry mouth, constipation, and paresthesia.
- The combination preparation of bupropion-naltrexone is not recommended as first-line therapy, but can be used for the obese smoker who desires therapy for smoking cessation and weight loss. Naltrexone is an opioid receptor antagonist used to treat alcohol and opioid dependence, and bupropion is used for depression and the prevention of weight gain during smoking cessation. The combination reduces weight by 4–5% compared to placebo. Side effects include nausea, headache, and constipation.
- The sympathomimetic drugs phentermine, diethylpropion, benzphetamine, and phendimetrazine are only approved for short-term treatment, up to 12 weeks. They reduce food intake by causing early satiety. Phentermine is the most widely prescribed weight loss drug; however, because of the potential side effects, potential for abuse, and limited duration of use, they are usually not recommended. They are contraindicated in patients with coronary artery disease, hypertension, and hyperthyroidism or in patients who have a history of drug abuse.

9.4 Bariatric Surgery

Candidates for bariatric surgery include obese patients with a BMI $\geq$40 kg/m^2 or patients with a BMI $\geq$35 kg/m^2 with at least one serious comorbidity, such as type 2 diabetes or hypertension. Adults with BMI between 30 and 34.9 Kg/m^2 can also be candidates if they suffer from uncontrolled type 2 diabetes or metabolic syndrome.

Bariatric surgical procedures cause weight loss through two main mechanisms: malabsorption and restriction. Some procedures have both components. Malabsorptive procedures shorten the length of the functional small intestine and decrease the absorption of nutrients. Restrictive procedures work by limiting the caloric intake by reducing the stomach's capacity.

- The Roux-en-Y gastric bypass (RYGB) is the most commonly performed bariatric procedure. It involves the creation of a small gastric pouch that is divided and separated from the distal stomach and anastomosed to a limb of small bowel. While it is mainly a restrictive procedure, it also has a malabsorptive component that participates in weight loss.
- The laparoscopic adjustable gastric banding is a restrictive procedure where an adjustable silicone ring is placed around the entrance of the stomach. Saline can be injected through an infusion port into the band to reduce its diameter, to increase the amount of restriction.
- Another restrictive procedure, the sleeve gastrectomy is a partial resection of the greater curvature of the stomach, which creates a tubular stomach. This procedure is easier to perform than the RYGB. The created tubular stomach is small and resistant to stretching due the absence of the fundus.

10 Conclusion

The impact of obesity on women's reproductive health is significant with harmful effects noted on the menstrual cycle, fertility, contraception, urinary incontinence, surgical risk, imaging studies, and certain malignancies. Weight loss is a difficult

but an achievable solution to many of these consequences. Weight loss can be achieved best in a multidisciplinary approach.

11 Cross-References

- Conservative Management of Endometrial Cancer
- Work Up and Management of Polycystic Ovary Syndrome

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Abnormal Vaginal Bleeding During the Early Reproductive Years

Anita L. Nelson

Contents

Abstract

New terminology was introduced by the Menstrual Disorder Working Group of the International Federation of Gynecology and Obstetrics (FIGO) and approved by ACOG several years ago to facilitate accurate descriptions of all dimension of each woman's bleeding. These descriptors better characterize abnormal uterine bleeding patterns than the older imprecise terms, such as "dysfunctional uterine bleeding" and "menorrhagia." The new PALM-COEIN classification system was implemented shortly thereafter to standardize reporting of *etiologies* of abnormal bleeding. Utilizing these new tools and current practice guidelines, this chapter will provide an overview of the differential diagnoses, evaluations, and treatment of women presenting with abnormal uterine bleeding from adolescence through the end of a woman's reproductive years.

Keywords

Abnormal uterine bleeding • Amenorrhea • Infrequent bleeding • Postcoital bleeding • Intermenstrual bleeding • Heavy menstrual bleeding • PCOS

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1 Introduction

Information about uterine bleeding is an essential vital sign for reproductive age women. At every clinical encounter, a woman should be asked about the normalcy and timing of her last menses. At initial and periodic well-woman visits, a full description of a patient's menstrual bleeding should be documented, including the frequency of her bleeding, duration of flow, volume of flow, and cycle-to-cycle variability. Table 1 shows the latest FIGO definition as well as normal values and acceptable words to use to describe abnormal patterns of bleeding. Self-characterization of bleeding, e.g., "irregular" versus "normal," is not sufficient; numerical estimates are needed (Fraser et al. 2011).

Abnormal uterine bleeding patterns range from complete absence of any uterine spotting to excessive and/or prolonged bleeding. Many different reproductive and general health conditions can result in abnormal bleeding, so evaluation should always be comprehensive. When a woman first complains of "abnormal bleeding," careful questioning can provide the information needed to describe her bleeding patterns utilizing the terms in Table 1 (Fraser et al. 2011). A through physical exam is needed because it may reveal the etiology of the abnormal uterine bleeding. At the end of a patient's first visit, the assessment includes the description of her menses using the FIGO terms, the differential diagnoses, and planned diagnostic studies as well medications for the woman to use as bridge therapy until her diagnosis is confirmed.

Once the results of diagnostic tests are available, the PALM-COEIN classification system (Table 2) should be applied to describe the cause of the patient's abnormal uterine bleeding (AUB) (Munro et al. 2011). Each of the letters in the PALM-portion of the PALM-COEIN mnemonic represents a structural (or anatomic) abnormality. These abnormalities are identified most frequently by pelvic exam, radiographic imaging, and/or biopsy. They include the following:

- Polyps can be reported on biopsy or visualized as endometrial thickening on ultrasound, but are better characterized with sonohysterography or hysteroscopy.
- Adenomyosis can be clinically suspected when a woman complains of heavy/prolonged bleeding with increased cramping and deep thrust dyspareunia just prior to menses. Palpation of the uterus at the time can reveal a globular texture to the uterus and uterine tenderness. Adenomyosis is usually best visualized on magnetic resonance imaging (MRI), although newer 3D ultrasonography can be used.
- Leiomyoma can be suspected on bimanual examination if the uterus is firm and possibly

Table 1 Menstrual parameters in the reproductive years

Clinical dimensions of menstruation and menstrual cycle	Descriptive term	Normal limits (5th–95th percentiles)
Frequency of menses, days	Frequent	<24
	Normal	24–38
	Infrequent	38
Regularity of menses: cycle-to-cycle variation over 12 months, days	Absent	No bleeding
	Regular	Variation ± 2–20
	Irregular	Variation >20
Duration of flow, days	Prolonged	>8.0
	Normal	4.5–8.0
	Shortened	<4.5
Volume of monthly blood loss, mL	Heavy	>80
	Normal	5–80
	Light	<5

Table 2 PALM-COEIN classification of abnormal uterine bleeding

PALM: structural causes	COEIN: functional causes
Polyp (AUB-P)	**C**oagulopathy (AUB-C)
Adenomyosis (AUB-A)	**O**vulatory dysfunction (AUB-O)
Leiomyoma (AUB-L)	**E**ndometrial (AUB-E)
Submucosal myoma (AUB-L_0)	
Other myoma (AUB-L_0)	
Malignancy and hyperplasia (AUB-M)	**I**atrogenic (AUB-I)
	Not yet classified (AUB-N)

enlarged and the contour is irregular. Leiomyomas are characterized by their position (intramural, submucosa, or subserosal) and size. Ultrasound can be used to identify leiomyoma, but MRI is more accurate at determining the location and volume of each lesion and may be the preferred test if the woman is considering embolization or myomectomy.

- Malignancy category includes all endometrial histological abnormalities from simple hyperplasia to premalignancies (endometrial intraepithelial neoplasia) to endometrial carcinoma (Munro et al. 2011). Endometrial biopsy is not routinely needed for low-risk women, but ACOG recommends biopsies for women with explained abnormal uterine if they have risk factors (ACOG Practice Bulletin No. 128, 2012). One large-scale retrospective study of over 1,500 women who underwent endometrial aspiration found that for women under 40 without obesity or diabetes, there was only a 1.1% chance endometrial sampling that would reveal evidence of significant (premalignant or malignant) disease (Nelson et al. 2016). Clinical judgment must be applied to sort out incidental noncontributing finding (such as a 1 cm intramural fibroid) from real causes for excessive bleeding.

The COIEN portion of the mnemonic represents functional or nonstructural etiologies. These include multiple gynecologic problems and non-gynecologic systemic diseases:

- Coagulopathies may be genetic (von Willebrand or excessive fibrinolytic activities) or acquired (platelet activation disorders) or result from severe sepsis or acute blood loss.
- Ovulatory dysfunction can result from genetic (amenorrhea of Turner syndrome), endocrinologic (androgen excess, thyroid dysfunction) or gynecologic (perimenopause) causes.
- Iatrogenic causes may be obvious (anticoagulants, copper IUDs) or more subtle (antihypertensive and antidepressant agents that affect dopamine production).
- Endometrial causes include functional abnormalities such as abnormal prostaglandin production, prostaglandin receptor imbalance, inappropriate activation of matrix metalloproteinases, or disruption of their tissue inhibitors.
- Not otherwise specified is self-explanatory.

The following sections will describe the most common bleeding abnormalities in adult premenopausal women and appropriate evaluation and recommended individualized treatments.

2 Secondary Amenorrhea

Secondary amenorrhea is defined in normally cycling women as the absence of any uterine bleeding or spotting for three consecutive cycles or, in women with baseline infrequent bleeding, as the absence of bleeding or spotting for two times their usual cycle length, but no longer than 6 months (Klein and Poth 2013). Secondary amenorrhea affects approximately 3–4% of reproductive-aged women. Pregnancy and lactational amenorrhea must always be excluded. Generally, amenorrhea is not considered to be a clinical problem when it is the desired result of therapy (e.g., endometrial ablation or progestin-only contraceptives). However, unexplained secondary amenorrhea can be concerning for a woman who has not completed her family and when it results from other health problems (e.g., renal failure, thyroid dysfunction). If the underlying cause for the woman's amenorrhea results in a lack of estrogen, secondary amenorrhea also presents concerns for long-term health risks associated with hypoestrogenemia – such as osteoporosis, dyslipidemia, and genitourinary problems. If the amenorrhea results from a lack of ovulation, then risks from unopposed estrogen (endometrial hyperplasia and cancer) must be addressed.

Secondary amenorrhea results from many different causes (Cox and Liu 2014). A complete history can help direct the work-up. Recent history of cervical procedures, such as LEEP or cone

Table 3 Secondary amenorrhea: conditions to consider

Anatomic defects
Asherman's syndrome (intrauterine synechiae, tuberculosis)
Cervical stenosis (iatrogenic)
Hypogonadism
Turner syndrome
Mosaicism
Premature ovarian insufficiency
Idiopathic
Injury: chemotherapy, radiation, mumps oophoritis, surgery
Hypothalamic causes
Excessive stress, extreme exercise, weight loss, eating disorders, pseudocyesis
Infection: TB, syphilis, encephalitis, sarcoidosis, neurotoxoplasmosis, AIDs
Chronic debilitating disease: wasting diseases (renal failure, hepatic failure, etc.)
Tumors: craniopharyngioma, germinoma, etc.
Traumatic brain injury
Pituitary causes
Tumors: hormone-secreting tumors (prolactin, ACTH, TSH, GH, etc.)
Empty sella
Necrosis – Sheehan syndrome: panhypopituitarism
Endocrine gland disorders
Autoimmune polyendocrine syndrome
Adrenal: adult onset (nonclassical) adrenal hyperplasia, Cushing syndrome, tumors
Thyroid myxedema
Ovarian tumors
Granulosa-theca cell, Sertoli-Leydig, thecoma, Brenner, cystic teratoma, cystadenoma, metastatic carcinoma, etc.
Uterine
Asherman syndrome (deliberate ablation; complication of infected dilation and curettage)
Receptor deficiency
Inflammatory/inflammation
Sarcoidosis, hemochromatosis
Other medical problems
Beta-thalassemia
Systemic lupus erythematosus
Rheumatoid arthritis
Myasthenia gravis
Dry eye syndrome
Malabsorption
Lymphoma
Histiocytosis
Clotting abnormalities

Table 4 Medications that decrease menstrual blood loss

Antidepressants
Antihistamines
Antihypertensives
Antipsychotics
Opiates
Cocaine

biopsy, suggests cervical stenosis, particularly if the woman continues to complain of monthly pelvic cramping. History of a dilation and curettage, especially in the face of infection, should lead to a work-up for Asherman's syndrome. A history of hemorrhage at delivery and a subsequent inability to breastfeed should raise concerns for Sheehan syndrome. Vasomotor symptoms and night sweats suggest perimenopausal hormonal changes. New onset severe acne or hirsutism can indicate an androgen-producing tumor in a woman of any age or adult onset (atypical) adrenal hyperplasia in a young woman. Headache or visual changes with spontaneous galactorrhea suggest pituitary tumor. Recent dramatic weight changes and/or excessive exercise or extreme stress often precipitates functional hypothalamic amenorrhea. Asian or Arab ethnicity can prompt an evaluation for beta-thalassemia. Other medical problems such as thyroid dysfunction, sarcoidosis, lymphoma, renal failure, and those listed on Table 3 need to be considered. Medication history in Table 4 can be very informative for both current drugs and prior use (e.g., chemotherapy, especially with cyclophosphamide, methotrexate, 5-flourouracil, and vismodegib). A history of prior infrequent menses is helpful since gradual changes in bleeding patterns suggest a different set of etiologies than does an abrupt cassation of menses.

A comprehensive physical examination is needed. Short stature with wide carrying angle suggests Turner syndrome. Skin changes can provide clues. Hirsutism, male pattern balding, or acne are consistent with excessive androgen production or sensitivity, while acanthosis nigricans is an indication of insulin resistance. A malar facial rash raises the possibility of systemic lupus erythematosus. Striae, buffalo hump, and

central obesity point to Cushing syndrome. Obesity by itself is more likely to cause infrequent, heavy bleeding, but in the extreme, a woman's bleeding may become so infrequent that technically the woman meets the definition of amenorrhea. Signs of genital atrophy support the diagnosis of estrogen deficiency. An enlarged, boggy, tender uterus is consistent with hematometra from cervical stenosis.

Laboratory testing should be guided by the findings from the history and physical examination. For example, a thyroid-stimulating hormone (TSH) test should be ordered. For a woman with fatigue, hair loss, weight gain, and delayed reflexes, severe hypothyroidism is more likely a cause of amenorrhea than other thyroid dysfunctions (Klein and Poth 2013).

> For women with no obvious etiology, the American Society of Reproductive Medicine (ASRM) recommends that once pregnancy and other obvious causes of amenorrhea have been ruled out, the work-up should start with TSH, follicle stimulating hormone (FSH) and prolactin levels (Practice Committee of ASRM 2008, pp. S219–25).

If TSH is abnormal, targeted therapies should be initiated to normalize thyroid function; endometrial protection should be provided until that goal is achieved. If prolactin is moderately elevated in the face of normal TSH levels, then a recreational drug/medication history may reveal the cause. If prolactin levels are greater than 70 mcg/mL, imaging (generally MRI) is needed to determine if there is a tumor of the anterior pituitary or an empty sella. If FSH is elevated, then additional hormonal testing (with repeat FSH, estradiol, and luteinizing hormone (LH) levels) is needed at least 1 month later to confirm the diagnosis of primary ovarian insufficiency with premature ovarian insufficiency (POI) (Cox and Liu 2014). If POI is diagnosed [high FSH, low estradiol] in the woman younger than age 30, karyotyping should be obtained because 13% of such women have abnormal karyotypes (ACOG. Committee Opinion No. 605 2014). Possible abnormalities include sex chromosome translocation and occult Y chromosome (which pose risks for gonadal tumors), fragile X syndrome, galactose-1-phosphate uridylytransferase (GALT) gene, FSH receptor genes, and other genes that may be clinically relevant to the woman and/or her children. If the woman with POI is over age 30, but younger than 40 years, she needs to be tested for autoantibodies associated with multiple endocrinopathies. If her amenorrhea has been caused by autoantibodies, she will need to be monitored over time for related endocrine failures, such as failure of her adrenal cortex, parathyroid, thyroid, and pancreas. POI may also result from chemotherapy (especially with alkylating agents or procarbazine) or radiation therapy (ACOG. Committee Opinion No. 605 2014).

If the FSH levels are normal or low, both PCOS and hypothalamic amenorrhea need to be ruled out. PCOS is discussed in detail in another chapter and summarized below. Hypothalamic amenorrhea is a diagnosis of exclusion when FSH and estradiol are low normal or low, but should be strongly suspected in the presence of low energy availability (with or without disordered eating), underweight, excessive exercise (athletic triad), or extreme psychological stress (Javed et al. 2013).

A progestin challenge test has been recommended in the past to distinguish between anovulatory etiologies (e.g., inadequate progestin) and those that cause estrogen deficiency (e.g., premature ovarian insufficiency). Today, it is recognized that the rates of both false positivity and false negativity with this test are excessive and that it should **not** be used as a diagnostic test. At best, progestin challenge test can help substantiate the diagnosis made by other tests; at worse it can lead to misdiagnosis. However, even though administration of progestin (daily treatment with MPA 10 mg or NETA 5 mg for 10–14 days) is not a diagnostic test, it may be very useful in terminating unopposed estrogen stimulation of the endometrium and should usually be administered

while the diagnostic tests listed above are being processed.

The initial objective in treating women with amenorrhea is to correct any underlying abnormality; for example, suppression of prolactin production, correction of thyroid dysfunction, or surgical excision of androgen-producing tumor can restore normal hypothalamic-pituitary-ovarian (HPO) axis function. Lifestyle changes including normalization of weight and moderation in exercise and stress management and cognitive behavior therapy can often provide long-term relief (Harrington et al. 2015). With chronic uncorrectable dysfunctions, hormonal balance must also be provided. For women with anovulatory cycles, at a minimum, periodic progestin therapy is needed. Those with estrogen deficiency need to have both estrogen and progestin restored. Higher doses that the typical doses used in menopausal women are necessary to prevent loss in these younger women with higher basal metabolic rates. Younger reproductive-aged women often prefer to use hormonal contraceptives in lieu of menopausal therapies. Addition of testosterone may be an effective adjunct for bone and muscle mass protection in women with POI if appropriate products are available. Measures to reduce cardiovascular risks must also be undertaken (Meczekalski et al. 2014). Contraception may also be important for women with premature ovarian insufficiency caused by autoantibodies, because nearly a quarter will show resumption of ovulation and 5–10% will spontaneously conceive if they rely on their ovarian insufficiency for birth control.

3 Infrequent Menses

Menstrual disorders are on a continuum. Many of the causes of amenorrhea described above can, in milder forms, cause infrequent bleeding. Some of the more common causes for infrequent bleeding include PCOS, prolactin disorders, thyroid dysfunction, and, less commonly, adrenal dysfunction. Abdominal fat accumulation represented by waist circumference is associated with infrequent bleeding in over 20% of women with simple obesity (De Pergola et al. 2009). Diabetes mellitus type 1 and type 2 are associated with infrequent menses; improved glycemic control improves cycling (Livshits and Seidman 2009). Infrequent bleeding can also be induced by drugs, such as dopaminergic, centrally-acting drugs and progestin treatments as well as by androgens (see Table 3).

Evaluation of a woman with infrequent bleeding proceeds much as outlined in the secondary amenorrhea section above with careful attention to elements in the history and physical examination that could point to the more easily recognizable causes. Initial laboratory testing is also similar. Lifelong infrequent menses may have different etiologies than new onset of infrequent bleeding. In a woman with no other etiology (thyroid dysfunction, androgen excess, etc.), matching her menstrual history and her weight over time can help confirm obesity-related dysfunction of the hypothalamic-pituitary-ovarian axis:

- Weight loss of only 5–10% using diet and exercise or bariatric surgery can often restore normal cycling and fertility – often at weights much higher than those at which the woman lost cycling during weight gain. This is important because some women rely on their weight-related amenorrhea for contraception and may experience unintended pregnancies after relatively slight weight loss.

A history of spontaneous galactorrhea should be investigated with serum prolactin levels. A scant amount of expressible galactorrhea is unlikely to affect menses, especially in women who have previously breastfed; routine testing of these women is rarely productive unless the woman is experiencing infertility.

A woman with infrequent menses should be asked about a history of any of the conditions listed in Table 3, since her current infrequent menses may lead to amenorrhea with time or with worsening of her condition. Lifestyle issues may be very telling especially for women who have eating disorders, exercise extensively, or

experience other stress. Once again, therapy should be targeted to the underlying cause, but endometrial protection and protection from unintended pregnancy must also be included in treatment plans.

Polycystic ovary syndrome (PCOS) is a syndrome that includes a broad variety of manifestations of ovarian dysfunction that may include menstrual irregularities, signs of androgen excess, and obesity. In addition to infertility, PCOS*See* Polycystic ovary syndrome (PCOS) is sometimes associated with acne, weight gain, hirsutism, thinning scalp hair, and higher lifetime risks for type 2 diabetes, high cholesterol, hypertension, and endometrial carcinoma. In 2004, the Rotterdam polycystic ovary syndrome consensus workshop codified guidelines for the diagnosis and management of PCOS. To be diagnosed with PCOS by the Rotterdam criteria, a woman must have at least two of the three criteria listed below and other conditions with similar signs, such as androgen-secreting tumors or Cushing's syndrome must be excluded (Rotterdam 2004). These three criteria include:

- Chronic anovulation (<8 menses per year)
- Hyperandrogenism (acne, hirsutism, temporal balding) or hyperandrogenemia
- Enlarged ovaries with at least 12 preantral follicles in each ovary (polycystic appearing ovaries (PAO))

The Rotterdam criteria created a definitional challenge because the third combination (criteria 1 and 3) is a meaningless tautology – all conditions causing chronic anovulation will induce polycystic appearing ovaries on ultrasound; many of these conditions have no relationship to androgen excess and are oftentimes found in young prepubertal girls, normally cycling women, oral contraceptive users, etc. To deal with these obvious definitional flaws, PCOS is being divided into subgroups based on different phenotypes. Each of these PCOS phenotypes has a different clinical presentation and different short- and long-term metabolic health risks that range from negligible to significant risks for cardiovascular disease and diabetes (Lizneva et al. 2016). The phenotype with the greatest long-term health risk is the group that meets all three of the Rotterdam criteria (Jovanovic et al. 2010).

The diagnosis of PCOS is predominantly a clinical one:

- History usually reveals a lifelong pattern of infrequent menses. However, some women develop "PCOS" later in life following significant weight gain. Anovulation can be suspected when women report no moliminal symptoms; they have no complaints of bloating, cramping, or other symptoms just prior to menses. In higher androgen states, menstrual flow is generally lighter. History of gestational diabetes is not uncommon.
- On examination, blood pressure, height, weight (BMI) and waist circumference should be measured. The presence of acne, hirsutism, androgenic balding, breast changes, and acanthosis nigricans is also suggestive.
- Laboratory testing is used to rule out other etiologies, not to diagnose PCOS. Gonadotropin levels are helpful only if history suggests premature ovarian insufficiency. Testosterone levels are generally ordered in practice to rule out tumors (total testosterone is quite adequate) and in research to monitor therapeutic response (free testosterone is often recommended despite its high cost and usual inconsistent results). Interestingly, today many experts now argue that testosterone levels are not necessary and may misclassify women if hyperandrogenism has been detected on physical exam (Tosi et al. 2016). DHEAs levels are usually not recommended in first-line evaluation, but can be useful for a markedly hirsute woman with normal testosterone levels. In woman under age 25 with hirsutism (especially rapidly progressive hirsutism), measurement of 17-hydroxy progesterone levels is indicated to rule out adult onset (atypical) adrenal hyperplasia. TSH may be appropriate if other symptoms or signs suggest thyroid dysfunction. Prolactin is routinely needed when spontaneous galactorrhea is found and when the woman

is seeking pregnancy. Tests for insulin resistance are not part of the work-up and are not helpful. However, glucose tolerance tests may be appropriate for woman's general health, especially in women with risk factors for diabetes. Similarly, fasting lipid panels may be clinically indicated to assess the woman's risk factor for cardiovascular disease (metabolic syndrome) for some PCOS phenotypes, such as obese women with androgen excess, but they are not needed to make the initial diagnoses of PCOS. Women with PCOS should be screened for mood disorders (especially depression) because those problems are more frequently found among women with this syndrome.

The goals of therapy for PCOS include reduction in the production and circulating levels of androgens, protection of the endometrium from unopposed estrogen, achievement of normal body weight, planning and preparing for pregnancy, and, where indicated, lowering of the risks for cardiovascular disease and diabetes. Treatment again focuses on correcting any identified problems. The goal may not be to restore cyclic monthly bleeding, especially if the woman appreciates the convenience of infrequent bleeding episodes; endometrial suppression is quite sufficient. Other interventions depend upon the woman's presenting symptoms and short-term childbearing plans. Usually lifelong, healthy lifestyles (especially weight loss and exercise) are strongly encouraged because excessive weight is often a problem and weight loss can be very challenging in women with "thrifty" PCOS metabolism. Selection of a diet comes down to finding a healthy diet that the woman can follow long term:

- Intriguingly, orlistat 120 mg given three times a day resulted in greater weight loss than metformin and reduced testosterone levels as well.
- In early experiments, lipid-lowering drugs have proven to be effective in reducing androgen excess and insulin resistance; however, more clinical work is needed before this therapy can be endorsed.

Various treatments for hyperandrogenism are available, generally involving estrogen-containing contraceptives with possible addition of an antiandrogen, such as spironolactone. Metformin is not generally recommended unless the woman has other indications, such as prediabetes. In fact, metformin is not considered to be first-line therapy, even when treating for women with PCOS for infertility (ACOG Practice Bulletin 108 2009; Legro et al. 2013).

4 Postcoital Bleeding

History is critical in identifying this bleeding abnormality. The two most common causes of postcoital bleeding are neoplasia (cervical polyps, cervical ectropion, cervical carcinoma) and cervical infection (chlamydia, gonorrhea, herpes simplex, trichomoniasis), but other causes, such as trauma and foreign bodies, must be considered (Tarney and Han 2014).While asymptomatic cervical polyps do not need to be removed, those that cause bleeding may harbor significant disease and warrant histological evaluation (Nelson et al. 2015).

5 Intermenstrual Bleeding

Spontaneous bleeding between menses is concerning for pregnancy and pregnancy complications in young women. In nonpregnant women, it can indicate endometrial disease, including malignancy. Occasionally, tubal carcinoma presents with chronic pink, watery vaginal discharge. Granulosa cell ovarian tumors can induce endometrial hyperplasia. Endometritis and more generalized pelvic infection are also classically listed as causes of intermenstrual bleeding, but usually women with these infections present with complaints of pain or discharge. Frequently in younger women, intermenstrual bleeding is iatrogenic – due to missed contraceptive pills, progestin-induced endometrial changes from intrauterine devices, implants, or injections – and does not need evaluation. Reassurance and treatment with nonsteroidal anti-inflammatory agents or

antifibrinolytic agents may help reduce the number of episodes and shorten the remaining ones.

> Unexplained intermenstrual bleeding, especially in women with risk factors for endometrial disease, requires evaluation of the endometrium. These risk factors include age (>45 years) and unopposed estrogen exposure (obesity, anovulatory cycling) (ACOG Practice Bulletin No. 128 2012).

Usually an office biopsy can provide the diagnosis (endometrial hyperplasia), but if the patient does not respond to therapy targeted to that diagnosis (e.g., progestin), she would need further work-up with either sonohysterography or hysteroscopically directed biopsy. If hyperplasia is diagnosed, the LNG-IUS 20 mg/24 h has been shown to be the most effective treatment (Gallos et al. 2010). Long-term therapy is needed because of the high rate of recurrence and progression to endometrial carcinoma.

6 Heavy Menstrual Bleeding

Nearly one in seven women reports having experienced heavy menstrual bleeding (HMB) at some point. Historically, heavy bleeding was defined as loss of more than 80 mL of blood each cycle because blood loss less than that amount did not result in anemia (Hallberg et al. 1966). HMB can lead to serious, even life-threatening anemia (Nelson and Ritchie 2015). It negatively impacts on a woman's quality of life and on her productivity. A classic analysis done over a decade ago estimated that women with HMB earn $1,692 less income each year. In addition, the cost of sanitary protections can be considerable. Women with HMB also utilize medical services at much higher rates than women with normal menses.

Accurate quantification of blood loss may be difficult in the clinical setting. In part, this may be because only 40–60% of total menstrual flow is made up of blood. In addition, differences in the absorbency and size of different sanitary protection products and variations in the fastidiousness and habits of individual women make it difficult to interpret the history. Symptoms of fatigue or dizziness may help support the diagnosis of resultant anemia.

Perception of normalcy often influences women's characterization of their flow. On the one hand, in Hallberg's study, nearly half of women who did have heavy losses (>80 mL) characterized their monthly flow as light or moderate and did not recognize that their loss was excessive. Prolonged bleeding is more easily diagnosed probably because it is more easily quantified than heavy blood loss. Surprisingly, many women who routinely have menstrual flow for more than 8 days frequently report it as "normal," often because many or all of the women in their families had similar bleeding patterns. Some women may think heavy or prolonged blood loss indicates higher fertility or femininity or more through "cleaning out" (Coutinho and Segal 1999). On the other hand, some women overestimate their losses. In Hallberg's classic study, over 30% of women who lost 20–40 mL of objectively measured blood characterized their bleeding as "heavy" (Hallberg et al. 1966). Fortunately, today the definition of HMB has been expanded to include women who lose less than an average 80 mL each cycle, but report their flow is heavy enough to interfere with their functioning. Sometimes this represents occasional heavy cycles, and sometimes it results from a short term (hours) of heavy bleeding during every cycle. Women in this group may not need extensive work-ups, but they certainly can be offered treatments that can reduce their bleeding. However, there are instances when a woman's blood loss may not meet the definitional threshold, but it is distinctly greater than losses she has experienced in the past. This may be an indication of new pathology and needs attention.

On physical examination, signs of anemia should be sought, such as pale conjunctiva or tachycardia. Examination should rule out obvious non-uterine sources of blood lose (large hemorrhoids). Iron deficiency anemia in a woman with a normal diet substantiates a woman's claim of

excessive blood loss, but it may be necessary to perform the hemoglobin testing at the end of menses that can detect their anemia.

Heavy menstrual bleeding is generally divided into two categories: acute excessive bleeding and chronic heavy menstrual bleeding.

6.1 Acute Heavy Bleeding

Hemodynamic stability must be quickly evaluated by symptoms and vital signs in women who present with acute heavy uterine bleeding. Acute rapid blood loss, even at higher levels of hemoglobin, is not as well tolerated as slow, chronic losses. Pregnancy tests and rapid point-of-care hemoglobin tests are needed to direct further actions.

Women who are not stable or who have signs of hypovolemia should receive fluids through large-bore IVs and blood transfusion with appropriate clotting factor replacement. A rapid abbreviated history should be conducted that includes information about the current bleeding episode (duration, flow, pain, and associated symptoms such as headache, palpitations, shortness of breath, dizziness, fatigue, pica, and past episodes (when, what diagnoses, what therapies) as well as any relevant medical problems that may cause losses (bleeding disorders, acute leukemia, immune thrombophilia purpura, aplastic anemia) and those be adversely impacted by anemia (diabetes, hypertension, cardiac disease). Recent surgical procedures (e.g., endometrial, cervical, or other uterine) should also be documented. Examination should first confirm that the source of the bleeding is uterine. Quick laboratory testing should include complete blood count, blood type and partial thromboplastin time, prothrombin time, activated partial thromboplastin, and fibrinogen. After the woman has been stabilized, evaluation should proceed as outlined below to arrest her bleeding, establish its etiology, and prevent future episodes.

Table 5 Medications that increase menstrual blood loss

Anticoagulants: warfarin, heparin
Antiepileptic agents: Dilantin, phenobarbital
Digitalis
Nonsteroidal anti-inflammatory drugs, including ASA
Contraceptives: copper IUD, steroidal hormones
Herbal agents: ginkgo, ginseng, motherwort

For women without life-threatening acute blood loss and those who have been stabilized, a more expanded history is needed. Details of the current episode of bleeding and any related symptoms should be expanded to include the past menstrual history and obstetrical and gynecology history. Information about medication use can be helpful especially if it contributes to bleeding (anticoagulants) or induces anovulation and unopposed estrogen (see Table 5). The woman should also be asked about any previous treatments she has been given to treat heavy bleeding. Family history of coagulation or thromboembolic disorders and any contraindication to medication usually used to treat HMB should be identified.

Physical examination should focus on physical findings suggestive of anemia, systemic disease (hepatic or renal failure, sepsis or hematopoietic cancers), endocrine disorders (thyroid), coagulopathy (bruising), and pelvic abnormalities (masses, evidence of trauma, or cervical or vaginal abnormalities that could account for the bleeding) (see Table 5).

Laboratory testing should be guided by the findings from the woman's history and physical examination. Thyroid-stimulating hormone, liver function tests, renal function tests, cervical infection tests, and iron reserve tests (serum iron, total iron binding capacity, and ferritin) may each provide important information for different clinical presentations.

Imaging tests (especially ultrasound and saline infusion sonography) may be helpful at some point to assess the PALM structural causes (see above).

Endometrial sampling to rule out endometrial disease should be performed after the woman is

stabilized in reproductive-aged women over 45 years and in younger women with a history of unopposed estrogen or a history of failed medical management of abnormal bleeding (ACOG Practice Bulletin 128 2012).

Most women with acute excessive bleeding will respond rather rapidly to appropriate medical therapy. However, in some cases, emergent surgical treatments may be required, especially if trauma is suspected. The procedures vary. Dilation and curettage may be needed to halt bleeding from retained products of conception or bleeding polyps; myomectomy is needed for an aborting fibroid; surgical repair may be needed for trauma. Emergency hysterectomy can be lifesaving in certain cases.

Medical therapy recommendations for acute bleeding have undergone evolution:

- Classically high-dose estrogen therapy has been recommended to be used to halt acute excessive bleeding. Intravenous conjugated equine estrogen is specifically approved by the US Food and Drug Administration for treatment of acute abnormal uterine bleeding (ACOG Committee Opinion 557 2013). Dosing regimens include 25 mg CEE IV every 4 h for unstable patients or 2.5 mg CEE orally every 4–6 h for 14–21 days for hemodynamically stable women. Progestin is generally added (MPA 5 mg once or twice a day) to support the endometrium 12–24 h after initiation of estrogen (when bleeding slows) and is continued until estrogen therapy is terminated. This approach mimicked the processes seen in the normal menstrual cycle. However, the only randomized, prospective, placebo-controlled study for a high-dose estrogen was a 5-h trial in which 17 women were given high-dose conjugated estrogen therapy and 17 received saline in an ER setting (DeVore et al. 1982). Intravenous estrogen is still the most common treatment prescribed for women who require hospitalization for transfusion and stabilization. However, women with iron deficiency anemia can often have reactive thrombocytosis This reactive thrombocytosis places the woman at higher risk for deep venous thrombosis and pulmonary embolism (Nelson and Ritchie 2015). Addition of high-dose estrogen increases that risk factor. However, progestin-only therapies outlined below have not been tested in the setting of acute bleeding.
- For outpatient therapy, high-dose estrogen-containing oral contraceptives have been the mainstay of therapy for decades, despite the fact that there is little in the literature to support any of the classically recommended regimens. Over time, the dose used in those regimens has been reduced to minimize the risk of thrombosis. The initial regimens popularized in textbooks called for 50 mcg ethinyl estradiol/30 mcg norgestrel oral contraceptives to be taken four times a day for 5 days (essentially a pill pack). Later regimens called for twice daily dosing for 5 days. Most recently, the recommendation is that two tablets of a 1/35 formulation be given the first day followed by one pill a day until the pill pack is finished (Fritz and Speroff 2011).
- In the largest randomized, comparative clinical trial for outpatient treatment of acute excessive uterine bleeding, Munro et al. demonstrated that medroxyprogesterone acetate (MPA) 20 mg taken orally three times a day for 7 days followed by MPA 20 mg taken once daily for an additional 21 days was at least as effective as high-dose oral contraceptives (one tablet 1/35 oral contraceptive taken three times a week for 7 days followed by any 1/20 formulation taken one tablet a day for 21 more days) in stopping bleeding, in avoiding surgery, and in achieving patient satisfaction (Munro et al. 2006). Although Munro's patients were all hemodynamically stable and treated as outpatients, the ACOG Committee Opinion on the topic does not restrict the use of this progestin-only therapy to outpatients (ACOG Committee Opinion 557 2013). The fact that progestin-

only approaches avoid VTE risk makes this their used first-line treatment option.

Medroxyprogesterone acetate (MPA) 20 mg taken orally three times a day for 7 days followed by MPA 20 mg once daily for an additional 21 days is a safe and effective treatment to stop acute bleeding with a wide range of endometrial pathology.

Some authorities have recommended using progestin when the endometrial lining is thickened and estrogen treatments when it appears to be atrophic. This recommendation assumes the clinician has access to imaging equipment, which may not be true in many settings. Furthermore, the imaging can add extra cost. Fortunately, in the largest prospective trial of management of acute bleeding in patients eligible for outpatient therapy, progestin-only therapy was very effective in all women. Bleeding was stopped in women with biopsy-proven atrophy as well as those whose endometrial sample revealed endometrial hyperplasia (Ammerman and Nelson 2013).

Once the acute bleeding has been arrested, it is important to ensure that future episodes are prevented. This can usually be achieved using therapies outlined for treatment of chronic heavy menstrual bleeding below.

6.2 Chronic Heavy Menstrual Bleeding

The goals of the work-up of heavy menstrual bleeding are to establish whether the heavy bleeding is due to a treatable organic disorder and whether the bleeding is ovulatory or anovulatory and to assess the burden the woman's symptoms place on her.

The history includes all the items described in the acute HMB section above. Iatrogenic causes, especially medications, need to be thoroughly evaluated (see Table 5). Serious medical conditions can also present with new onset or chronic heavy menstrual bleeding. Women who have renal insufficiency approaching anuria experience very heavy bleeding. Once renal failure is complete, these women become amenorrheic. However, after dialysis is started, they again may experience very heavy menses. These losses are very significant, because the woman has no ability to stimulate production of red blood cells with erythropoietin. With loss of vitamin K in hepatic failure (liver cirrhosis or active hepatitis), women can develop heavy menses. Hypersplenism and adrenal hyperplasia can also cause HMB. As noted earlier, endocrine abnormalities (thyroid myxedema) can induce heavy bleeding. For women with hematopoietic carcinoma, heavy bleeding can be their first symptom.

Physical examination would include vital signs (including BMI); thyroid exam; tests for abdominal tenderness, hepatomegaly or abdominal distention, striae, skin bruising, petechiae, and pallor; and pelvic exam. Imaging studies can be selected based on the woman's history, and exam findings to define any structural/anatomic causes (PALM) as described above.

The function causes (COIEN) summarized above must also be evaluated.

In recent years, there has been a growing awareness that coagulopathies are very common in women of any age. Whenever other etiologies are not identified, it is necessary to evaluate the ability of the woman to form clots and to maintain them. Some bleeding disorders are classically genetic (von Willebrand disease, some forms of thrombocytopenia), but many are acquired. Inherited bleeding disorders are found in 10–20% of adult women with objectively verified heavy menstrual bleeding. In one study of 115 women with idiopathic heavy menstrual bleeding, 47% were found to have a hemostatic abnormality, the most common of which was acquired platelet aggregation defects (44%). Platelet disorders can include abnormal numbers of platelets (ITP or leukemia) or disorders of platelet function (Philipp et al. 2005). In a subsequent study, bleeding disorders were found in 31% of women with HMB (average PBAC of 271) and platelet disorders accounted for 69% of

those cases; von Willebrand was a distinct second at 22% (Knol et al. 2013). Philipp et al. have developed a detailed screening tool to detect bleeding disorders in women with heavy menstrual bleeding (Philipp et al. 2011). This diagnosis is often overlooked; in a survey of over 500 OB-GYNs, only 38.8% said that they would consider bleeding disorders for adult women with HMB:

- ACOG recommends screening for an underlying disorder of hemostasis in an adult woman if she has had heavy menstrual bleeding since menarche, and she has experienced excessive blood loss postpartum, with surgery or with dental work, and she has had at least two of the following conditions: nose bleeds one to two times per month, frequent gum bleeding, and family history of bleeding symptoms (ACOG Adolescent Committee Opinion 580 2013). The initial work-up recommended is a CBC with platelet count, PT, PTT, and possible fibrinogen. Specific tests for von Willebrand are also listed; either ristocetin cofactor assay or antigen testing is generally recommended as screening test. Specific von Willebrand defects require more detailed testing, usually best done by hematologist [x ref. Committee Opinion 580].

Ovulatory dysfunction is one of the most easily diagnosed conditions. Usually a menstrual history is sufficient, but hormonal testing can be helpful in identifying medical conditions underlying the menstrual disorder (see above). Anovulatory bleeding can be heavy for several reasons involving the endometrial environment. Unopposed estrogen stimulation induces thicker endometrial layer; endometrial sloughing is dyssynchronous and, therefore, prolonged. Without ovulation, the levels of $PGF_{2\alpha}$ responsible for vasoconstriction do not rise in the "luteal phase" to exceed the levels of PGE_2 responsible for vasodilation. Abnormalities can also occur in the balance in production of thromboxane (promotes platelet aggregation promotion) and prostacyclin (inhibits platelet aggregation). In ovulatory women with HMB, similar imbalances can be seen because of abnormal prostaglandin synthesis and/or increased numbers of receptors. Diagnosis of these problems has to be clinical; response to NSAIDs helps support the diagnosis.

Targeted therapies are needed to treat heavy menstrual bleeding due to systemic diseases. For example, excessive bleeding due to thyroid dysfunction requires only temporary menstrual suppression until euthyroidism can be restored. Endometrial polyps can be excised. Women with underlying disordered hemostasis will need targeted therapy with agents such as DDAVP (desmopressin acetate) as outlined in Management Guidelines from the National Health, Lung and Blood Institute. Treatment of endometrial hyperplasia is covered in other chapters. However, for a woman with chronic conditions, such as bleeding diatheses, hypersplenism, bone marrow suppression, as well as those with uterine abnormalities, such as leiomyoma or adenomyosis or idiopathic heavy menstrual bleeding, two questions need to be answered to determine her best treatment options:

- Is she seeking pregnancy?
- How excessive is her blood loss? (or how much of a reduction does she need?)

6.3 Medical Therapies for Chronic Heavy Menstrual Bleeding

For women seeking pregnancy and for women who need only slight reductions in their blood loss, nonhormonal methods may be offered. In this case, nonsteroidal anti-inflammatory agents (NSAIDs) taken at high enough doses at appropriate intervals reduce blood loss by 20–30% (Lethaby et al. 2013). One typical regimen is ibuprofen 800 mg orally every 8 h from onset of menses until end of heavy flow (up to 5 days). Antifibrinolytic agents can reduce blood loss about 40% (Freeman et al. 2011). A typical treatment would include Lysteda 650 mg, two tabs orally, three times a day starting at the onset of bleeding and continuing through the last day of heavy flow (but not more than 5 days). These agents have the advantages that they do not affect

fertility and they are used only at the time of menses.

For women who are not seeking pregnancy, endometrial suppression can provide significant reductions in menstrual blood loss even though for many of them, such use would be off-label. Usually first-line therapy is medical [combined hormonal contraceptives, progestin-only pills, injectable progestin contraceptives, LNG-IUS-20 mg/day, cyclic oral progestin). Surgery should generally be reserved for those who have other pelvic pathology and those whose bleeding is not medically controlled (infra vide). Unfortunately, in a recent study of over 2,200 women who underwent hysterectomy for benign conditions in 2013, over one-third of the cases had no documentation that any medical treatments had been used prior to surgery (Corona et al. 2015).

Hormonal contraceptives are the therapy most frequently prescribed to control heavy bleeding. Traditionally oral contraceptives, contraceptive patches, and contraceptive vaginal rings have been used cyclically to reduce the amount of scheduled bleeding by 50–70%. Extended cycle (AKA continuous) use of oral contraceptives or vaginal contraceptive rings has been shown to reduce endometrial thickness and to substantially reduce the total numbers of days of scheduled bleeding even further (Edelman et al. 2014). Extended use of the current transdermal patch is not recommended given the increasing estrogen levels associated with its prolonged use. One oral contraceptive pill has been approved by the FDA for treatment of heavy menstrual bleeding; the multiphasic desogestrel/estradiol valerate pill reduced heavy menstrual bleeding almost as well as the high dose LNG-IUS did in its pivotal clinical trial (Kaunitz et al. 2010; Wasiak et al. 2013).

Despite decades of clinical experience utilizing DMPA to achieve amenorrhea, there is very little in the literature about its use to treat heavy menstrual bleeding. There is evidence that DMPA is useful in preventing recurrent hemorrhagic ovarian cysts in women on chronic anticoagulation therapy, and DMPA was shown to reduce blood loss among 20 women with uterine fibroid-associated HMB. DMPA in conjunction with GNRH agonists has been helpful in treating women at risk for severe thrombocytopenia from myelosuppressive therapy for cancer. One recent review concluded that DMPA use was not contraindicated for use by women with inherited bleeding disorders. Although menstrual blood loss diminishes with longer-term contraceptive implant use, its unpredictable impact on bleeding discourages the use of the implant to treat HMB. GnRH agonists can be used short term to suppress estrogen protection and endometrial growth. Usually add-back therapy is used for longer-term use to reduce the associated estrogen deficiency symptoms and adverse reactions on bone health (Bradley and Gueye 2016).

The LNG-IUS-20mcg/24 h is the most effective medical therapy for idiopathic heavy menstrual bleeding (Bitzer et al. 2015; Lethaby et al. 2015). In the comparative open-label randomized trial against luteal phase MPA 10 mg per day, this LNG-IUS reduced blood loss by at least 50% and normalized blood loss to <80 mL in every episode in 85% of subjects (Kaunitz et al. 2010). Women with leiomyoma <4 cm which protruded into the endometrial cavity <50% of their diameter were included in the study. Subsequent studies have shown LNG-IUS superior to different medical comparators (NETA, tranexamic acid, mefenamic acid) for treatment of idiopathic HMB (Kiseli et al. 2016) and for HMB due to adenomyosis (Shaaban et al. 2015). Women who are on anticoagulant therapy also benefited from LNG-IUS-20 by increasing hemoglobin levels (Vilos et al. 2009). The ECLIPSE study found the LNG-IUS to be superior to other medical therapies, but only for the first 3 years (Gupta et al. 2015):

- The most recent Cochrane Review also concluded that compared to endometrial ablation, satisfaction rates and quality of life measures were similar, but the LNG-IUS was more cost-effective. Another advantage is that the LNG-IUS also provides contraceptive protection. This same review concluded that the LNG-IUS was less effective than hysterectomy in reducing HMB, but quality of life was improved by both. The LNG-IUS appears to be more cost-effective than hysterectomy for

up to 10 years after treatment (Lethaby et al. 2015). This last point was substantiated in a 10-year study of women randomized to hysterectomy vs. LNG-IUS, which showed that over half of the women in the LNG-IUS arm avoided having that surgery.

Most recently ulipristal acetate 5 mg orally each day has been shown to rapidly and effectively control heavy menstrual bleeding preoperatively for women with leiomyoma (Donnez et al. 2014). Early clinical trials with ginger extracts showed greater decrease in blood loss than was seen with placebo (Kashefi et al. 2015).

6.4 Surgical Therapies for Heavy Menstrual Bleeding

Surgical options are also available, but generally are reserved for situations when medical therapies are inappropriate or inadequate. For women with heavy menstrual bleeding, endometrial ablation scarifies the endometrial lining. Endometrial ablation techniques have diversified over time to provide flexibility and accommodate different endometrial configurations. Electrical or electrocautery ablation, hydrothermal ablation, balloon therapy, radio frequency, cryoablation, and microwave ablation techniques all have roughly equivalent efficacy and satisfaction rates (Angioni et al. 2016). Initially introduced as a less invasive surgical option, which could reduce hysterectomy rates, its use flourished. Success rates for amenorrhea/normalization of blood loss are reported to be 80% after one procedure; some will undergo a repeat ablation and about 10–15% of women ultimately undergo hysterectomy. Although there are infrequent procedure complications, there are two important caveats associated with ablation. First, the endometrium must be thoroughly assessed to rule out malignancy and premalignant conditions prior to ablation. Second, the woman must also be protected against pregnancy until menopause.

For women with limited numbers of leiomyoma causing their excessive bleeding, uterine artery embolization and myomectomy may be options. In a 10-year follow-up study of women randomized to embolization, two thirds avoided hysterectomy (de Bruijn et al. 2016). Laparoscopic myomectomy may be helpful in wishing to preserve fertility. Often women will need to have cesarean delivery following myomectomy, especially if the endometrial cavity is entered during the surgery.

Hysterectomy is a definitive treatment for heavy menstrual bleeding, but it can cause severe complications for a small minority of women (Marjoribanks et al. 2016). Less invasive surgical approaches (laparoscopy, robotic surgery) significantly reduce recovery time for women.

7 Conclusions

Uterine bleeding patterns are a primary vital sign of a woman's reproductive health. Abnormal uterine bleeding is most common at the extremes of reproductive life (puberty and perimenopause), which is discussed in other chapters. Abnormal bleeding patterns that manifest during the reproductive years warrant evaluation and usually therapy. The FIGO terminology should be used in each case to fully describe all the dimensions of the woman's bleeding (its frequency, duration, volume, and variation). The PALM-COEIN classification system for abnormal uterine bleeding provides a shorthand, uniform system of diagnosis that can improve visit-to-visit communications. The spectrum of abnormal uterine bleeding patterns includes both disorders of amounts (amenorrhea to heavy and prolonged bleeding) and timing disorders (postcoital, intermenstrual bleeding).

Infrequent bleeding and secondary amenorrhea can represent problems anywhere along the hypothalamic-pituitary-ovarian (HPO) axis, within the uterus, or the secondary effects of systemic disease or medications on that HPO axis. Work-up should be guided by the history and physical findings. Comprehensive broad-based evaluation strategies have been described that are very time efficient. However, they are often not cost-effective. Therapies should target the underlying cause, but should also normalize sex

steroid levels and protect end organs (endometrium, bone) that are affected by those abnormalities.

Heavy bleeding can result in serious, even life-threatening anemia; more commonly it can significantly diminish a woman's quality of life and her productivity. Acute bleeding usually commands attention, but chronic excessive losses may not be appreciated as a health problem until anemia develops. Heavy bleeding can have structural causes (PALM) and/or functional causes (COEIN). Systemic disease and medications can impact on bleeding by directly impacting uterine and endometrial factors or by altering the function of the HPO axis. Attention first focuses on correcting the woman's underlying pathology, but endometrial suppression, usually with hormonal contraceptives, NSAIDs, or tranexamic acid are first-line therapies. Both versions of the LNG-IUS-20 mg/24 h are also very effective, first-line therapies for idiopathic chronic HMB. Other hormonal methods, including DMPA or NETA suppression, offer alternatives that can be very effective when used as directed.

It is important to educate women about normal patterns of menstrual bleeding so they can help identify early abnormalities in their patterns that may represent significant pathologies. In this setting, clinicians should reassure women about the health benefits of endometrial suppression (iatrogenic amenorrhea) provided by progestin-only or extended cycle combined hormonal therapy. This apparent mixed messaging requires skill and time, but is very important to the long-term success of such therapies and to the health of patients.

Procedural therapies have also increased in popularity. Endometrial ablation is possible using a wide range of techniques. Uterine artery embolization may be very effective when dealing with HMB if only a few leiomyomas require treatment. Myomectomy is attractive to women wishing to preserve their fertility if bleeding is due to few myomas. Hysterectomy is reserved for women with pelvic pathology and for those who are not candidates for or do not respond to appropriate medical treatments. The potential role of newer agents, such as ulipristal acetate, is being explored.

8 Cross-References

▶ Work-up and Management of Polycystic Ovary Syndrome

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Sexually Transmitted Diseases: Diagnosis and Work-Up (GC, Chlamydia, Herpes HPV)

Antonio V. Castenada

Abstract

There is an array of tests available to diagnose each of the above sexually transmitted diseases. Each test has its own sensitivity, specificity, and specific clinical situation for which it is ideally situated. Nucleic acid amplification tests (NAATs) tend to have the highest sensitivity and specificity when testing for gonorrhea and chlamydia. However, depending on the clinical scenario and site to be tested, there may be other tests which are better suited. Testing for HSV lesions has variable sensitivity and specificity based on the time interval between testing and outbreak and amount of viral shedding. To negate this variability, indirect testing which exams the patient's blood for antibodies to HSV has been created. This test can detect antibodies against HSV, even after lesions have resolved. The human papillomavirus is extremely prevalent worldwide. Cytology and HPV co-testing still remain the gold standard for diagnosing and triaging HPV. A thorough knowledge of the common presentation, available testing, and current treatments is essential for all healthcare providers. Early detection, diagnosis, and treatment will prevent continued spread to other parties and decrease morbidity in patients.

The purpose of this chapter is to present the current standards for diagnosis and treatment of sexually transmitted diseases. In this text, presentation, diagnosis, and treatment of the sexually transmitted diseases, gonorrhea, chlamydia, herpes simplex virus, and human papillomavirus, are discussed. In order to obtain the most current and accurate data, a comprehensive literature review was performed for each of the abovementioned sexually transmitted diseases in regard to presentation, available screening and diagnostic testing, and treatment. The CDC database was cross-referenced to confirm concordance in the treatment of the abovementioned sexually transmitted diseases.

Keywords

Gonorrhea • Chlamydia • Human papillomavirus • Herpes simplex virus • Screening • Sexually transmitted infections

Contents

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1 Introduction

According to the Centers for Disease Control and Prevention in 2008, there was an estimated 20 million new cases of sexually transmitted diseases diagnosed, with a prevalence of 110 million. The estimated healthcare cost for treatment and diagnosis of these diseases was approximately $16 billion. The breakup of disease burden is roughly equal for men and women. The prevalence of disease is highest in those 30 years of age and younger. Many of the most prevalent sexually transmitted diseases such as gonorrhea and chlamydia have effective treatments available that prevent major complications. If untreated, the infection may progress and cause tubal damage, require extended antibiotic treatment, or even become life threatening. For this reason, it is imperative that the clinician be aware of the appropriate screening and diagnostic tests available to identify sexually transmitted diseases. Often patients are asymptomatic. For this reason, routine screening of individuals at risks for sexually transmitted disease is encouraged. The indications for screening are listed below (CDC 2013) (Table 1).

2 *Chlamydia trachomatis*

2.1 Epidemiology

Chlamydia is the second most prevalent STD in the United States with the highest prevalence in less than 25 years of age group. Given the asymptomatic nature of the disease for a majority of women and the high prevalence, yearly testing is advised for women less than 25 years old. Screening should be done in all women less than 25 years old and in women over 25 years of age with any of the following risk factors: new or multiple sexual partners, inconsistent condom use, sex worker, current STD, or history of STDs (Williams 2012). While infections are often asymptomatic, symptoms can include mucopurulent discharge, endocervical secretions, and hyperemia of the infected tissue/edema. If the infection affects the urethra, urethritis is common and often associated with prominent dysuria, frequency, and/or urgency (Williams 2012). Untreated chlamydial infections can lead to serious complications such as pelvic inflammatory disease (PID), subsequent infertility, and increased risk of ectopic pregnancy. The implementation of routine screening of women 25 years old and less has led to a decrease in serious complications such as PID. Currently, there are no suggestions for the routine screening of asymptomatic men (CDC 2015a).

2.2 Screening and Testing

There are many tests available to screen and diagnose chlamydia. The most often used tests include the use of nucleic acid amplification tests (NAATs), direct fluorescent antibody (DFA), enzyme immunoassay (EIA), and tissue culture (Carder et al. 2006). Testing for chlamydia relies heavily on the use of NAATs given their high sensitivity and fast turnaround time.

Table 1 Indications for sexually transmitted disease screening

Sexually transmitted disease	Indications for screening	Risk factors	Treatment
Chlamydia trachomatis	Age 25+ with risk factors	Prior STI; new partner, multiple partner, sex work, intercourse without condoms	Azithromycin 1 g po × 1
	Under age 25		
	Women with cervicitis		
	All pregnant women in first trimester, again in third trimester if high risk		
Neisseria gonorrhoeae	Age 25+ with risk factors, under age 25	Prior STI; new partner, multiple partner, sex work, intercourse without condoms	Ceftriaxone 250 mg IM × 1 + azithromycin 1 g po × 1[a]
Herpes simplex virus	Not indicated [only if a suspected lesion is present or if partner has HSV]	Number of sexual partners	Acyclovir 400 mg po TID × 7–10 days (and others)
Human papillomavirus	Reflex testing for women age 21–30 every 3 years or routine screening age 30–65 every 5 years	Number of partners	None
		Age of first intercourse	

[a]Adapted from Williams Gynecology 2nd edition; Chapter 1 Well Woman Care; Patient Education Fact Sheet, New Guidelines for Cervical Cancer Screening, Sept 2013

NAATs have the ability to produce a positive signal from a single copy of RNA or DNA. This has led to their high sensitivity, especially when compared to other forms of testing; however, no test can give 100% sensitivity (Carder et al. 2006). Given the high sensitivity of NAATs, there is only another NAAT sensitive enough to confirm a positive result. If test results are equivocal, then the original sample should be retested rather than collecting a new specimen. NAATs can be used for a variety of locations including first-catch urine specimens, cervical, urethral, and rectal:

- Tissue culture is the preferred test for rectal specimens but when unavailable NAATs are the test of choice (Carder et al. 2006).

DFAs use fluorescent-labeled antibodies that bind to *C. trachomatis*. Typically a swab is used to sample the sites suspicious for *C. trachomatis*. Following sampling, the swab contents are placed on a slide and allowed to dry. In the lab, antibodies that bind to *C. trachomatis* are then placed over the sample and the slide is viewed under a fluorescence microscope. Visualization of florescence yields a positive result, while absence of florescence yields a negative result. Sensitivity and specificity are dependent on the laboratory:

- Given that DFAs must be viewed individually under a microscope, DFAs are best suited for detecting *C. trachomatis* in small number (Carder et al. 2006).
- DFAs can be used to detect *C. trachomatis* from cervical, urethral, pharyngeal, and rectal specimens. DFAs can be used with first-catch urine but it is not ideal.

EIAs use monoclonal and polyclonal antibodies labeled with an enzyme to detect the specific lipopolysaccharide within *C. trachomatis*. If present, the enzyme converts a colorless substrate into a colored product that is then detected by using a spectrophotometer. The antibodies in this EIAs can cross-react with other microorganisms that contain LPS such as other *Chlamydia* species.

When an EIA yields a positive result, confirmatory testing should be done by either DFA or using a blocking antibody that has been developed to verify positive EIA rest results. Sensitivity for EIA is less than that for DFA (Carder et al. 2006). EIAs can be used to collect specimens from cervical and urethral specimens and in first-catch urine from symptomatic men.

Tissue culture for *C. trachomatis* is now a test with limited use in clinical practice. This was previously the traditional gold standard for testing. However, with the advent of new tests such as the NAATs, DFAs, and EIAs, there are very few laboratories that will still perform tissue culture for *C. trachomatis* given that cell cultures are very labor intensive and expensive and take several days for a positive result:

- There are several instances when culture is the preferred testing method. In cases of sexual assault or abuse, tissue culture is the preferred method because it allows clinicians and law enforcement agencies to definitively identify the organism causing the infection.
- In addition, tissue culture is the test of choice in diagnosing *C. trachomatis* from rectal specimens.
- Tissue culture is suitable for specimens collected from the cervix, urethra, and pharynx, but given the aforementioned limitations, it is not routinely used (Papp et al. 2014).

Test of cure (TOC) is not routinely done if the patient has been treated, if there is confirmation that the patient complied with treatment, and if there is no risk of reinfection. If the clinician is in doubt, a TOC should be performed. Given the morbidity associated with *C. trachomatis* to the developing fetus, TOC should be routinely done in all pregnant patients. TOCs are typically completed 3–5 weeks posttreatment. TOC performed sooner can cause false-positive results secondary to residual RNA or DNA from the organism:

- CDC recommends that clinicians contact local or state health department for guidance to arrange for antimicrobial susceptibility from patients failing treatment with CDC-recommended regimens. Ideally, TOC and evaluation of antibiotic efficacy can only be performed via tissue culture. NAATs and DFAs are not FDA approved for this purpose (Papp et al. 2014).

2.3 Sites for Testing

Given the numerous mucosal surfaces that *C. trachomatis* can infect and the numerous tests available to screen and diagnose *C. trachomatis* infections, it is imperative that the clinician be familiar with which tests are appropriate to use with each site of testing (summarized in Table 2):

- First-catch urine is one of the simplest samples to collect. Ideally the urine specimen should be collected from the first 30 cc of urine. NAATs are the preferred method of testing for first-catch urine. EIAs are highly sensitive in the symptomatic male but not in asymptomatic males or females in general. If NAATs are unavailable, DFA can be used but are not ideal. Culture of first-catch urine is typically not appropriate.
- Cervical and urethral specimen sites are suitable for all the abovementioned testing modalities.
- Vaginal swabs can be collected by either the physician or the patient. Studies have shown high sensitivity when vaginal swabs are tested with NAATs with sensitivity >95%. The sensitivity in physician- vs. patient-collected

Table 2 Sample collection site for *C. trachomatis*

Testing site	Approved methods
Urine (first 30 cc's)	NAATs
	EIAs in male urine
Vaginal	NAATs
Cervical	NAATs, DFAs, EIAs, culture
Oropharynx	Culture
	DFAs-acceptable
Rectal obtained via proctoscopy	Culture
	DFAs-acceptable
Urethral	NAATs, DFAs, EIAs, culture

vaginal specimens was not statistically significant. Several studies demonstrated a higher sensitivity in vaginal specimen than endocervical specimen (95% vs. 90%). In addition, patient-collected vaginal swabs are better tolerated by the patient and provide less discomfort, especially in the pediatric and adolescent age groups (Schachter et al. 2005).

- Given the recent changes of sexual practices, the oropharynx and rectum are being found to be sites of infection with *C. trachomatis* more commonly. The oropharynx and rectum are best tested with culture or DFA (Carder et al. 2006).

2.4 Treatment

There are many treatment regimens available for chlamydia. The main concerns for treating chlamydia is early intervention to reduce the risk of PID, patient compliance, abstinence during the treatment window, and treating of infected partners. In the pregnant population, early treatment has been shown to decrease the risk of transmission to the neonate/fetus:

- In patients whom compliance to treatment is of concern, azithromycin 1 g orally onetime dosing has been proven to treat chlamydia and is considered a first-line treatment. In patients who are unable to tolerate azithromycin secondary to allergies or side effects, doxycycline 100 mg orally twice daily for 1 week has been proven to be equally as effective (98% and 97% response rates, respectively) (CDC 2015a).
- A 200 mg po extended release daily doxycycline regimen has been tested and found to be equally as effective as the 100 mg twice daily regimen, but is considerably more expensive. Doxycycline is contraindicated in the second and third trimester of pregnancy; for this reason, treatment with azithromycin is the preferred method of treatment.
  - Given the risk to the neonate in the instance when chlamydia is not completely treated, a test of cure is recommended 3–4 weeks after completing treatment (CDC 2015a).
- Other treatment regimens are available such as erythromycin 500 mg orally four times daily for 7 days or levofloxacin/ofloxacin for a 7-day course. Treatment with erythromycin is not as effective as azithromycin and has been associated with more gastrointestinal side effects.
- Levofloxacin and ofloxacin are also effective in the treatment of chlamydia but are relatively more expensive and have not shown any superiority to treatment with azithromycin or doxycycline. For this reason, azithromycin and doxycycline are considered first-line treatments (CDC 2015a) (summarized in Table 3).

One aspect of treatment of chlamydia is patient education. It is imperative to educate the patient about risk of reinfection if their partner is not treated, informing all sexual contacts so that they may be treated as well, and for patients to abstain from sexual intercourse for 7 days after receiving onetime treatment or to abstain from sexual intercourse for the entire treatment duration for the 7-day antibiotic course and to wait for symptoms to resolve. Failure to comply with the above greatly increases the risk of reinfection (CDC 2015a).

2.5 Expedited Partner Therapy in Management of Chlamydia and Gonorrhea Infection

> The American College of Obstetricians and Gynecologists [ACOG] supports the use of expedited partner therapy when a patient's partner is unwilling or unable to seek medical care. ACOG recommended that therapy should be accompanied with treatment instructions along with a recommendation that they seek medical attention as soon as possible. (ACOG Committee Opinion 2015)

Table 3 Treatment of chlamydia

Treatment	
Azithromycin 1 g po ×1	First-line treatment
Doxycycline 100 mg po BID ×7days[a]	First-line treatment
Erythromycin 500 mg po QID ×7 days	Second-line treatment
Erythromycin ethylsuccinate 800 mg po QID ×7 days	Second-line treatment
Levofloxacin 500 mg po ×7 days	Second-line treatment
Ofloxacin 300 mg po BID ×7 days	Second-line treatment

[a]Delayed release 200 mg po doxycycline regimen ×7 days has been studied and is equally efficacious, but more expensive

3 *Neisseria gonorrhoeae*

3.1 Epidemiology

Neisseria gonorrhoeae is a gram-negative diplococcus bacterium which is transmitted through sexual activity. According to recent CDC publications, it is estimated that there are approximately 700,000 new cases of gonorrhea every year in the United States, making it the second most common bacterial sexually transmitted disease (Bleich et al. 2012). Gonorrhea is often asymptomatic or only presents with odorless white/yellow vaginal discharge. Other symptoms of gonorrhea include abnormal vaginal discharge, abnormal vaginal bleeding after intercourse, intermenstrual spotting, genital itching, and pain. Gonorrhea can cause ascending infections in the female genital urinary tract and systemic illness. Systemic gonorrhea, also known as disseminated gonococcal infection, has a prevalence reported as high as 0.5–3% after untreated mucosal infection (Bleich et al. 2012). Initial symptoms can present with fevers, arthralgia, rash, migratory polyarthritis, septic arthritis, and tenosynovitis. Severe cases of disseminated gonococcal infection can result in endocarditis and meningitis (Bleich et al. 2012).

Compared to women, a larger percentage of men are symptomatic from *N. gonorrhoeae* infection that often leads to earlier treatment before sequel, but typically not before transmission has occurred. Women typically are asymptomatic at initial time of infection and may later present with pelvic inflammatory disease (PID) associated with *N. gonorrhoeae* infections. PID can lead to hospitalization, scarring of the fallopian tubes, and future increased risk of ectopic pregnancy or infertility. For these reasons, accurate and rapid diagnosis of gonorrhea is critical in the healthcare setting.

Given the asymptomatic nature of the disease in a majority of women and high prevalence, yearly testing is advised in women less than 25 years of age. Screening should be undertaken in all women less than 25 years old or if any of the following risk factors: new or multiple sexual partners, inconsistent condom use, sex worker, current STD or history of STDs, or previous infection with *N. gonorrhoeae* (Williams 2012).

3.2 Screening and Diagnostic Testing

There are various forms of testing available for screening and diagnosing gonorrhea including microscopy, culture, nucleic acid amplification tests, and nucleic acid hybridization test. These tests are commonly used in the healthcare setting and each has their preferred site of testing and particular advantages:

- Direct microscopy has both high sensitivity and specificity in the symptomatic patient population (95%, 99%). The identification of gram-negative intracellular diplococci and polymorphonuclear leukocytes on microscopy is considered diagnostic for gonorrhea. The sensitivity of direct microscopy is greatly decreased in the asymptomatic patient population. When used in patients who are asymptomatic as a screening tool, the sensitivity is only 50–75%. However, the specificity of direct microscopy remains about 99% in both the symptomatic and asymptomatic patient populations (CDC 2015a).
- Culture has long been used for testing of gonorrhea. Culture has many advantages, one

being that it can use specimens from all sites as long as there are viable organisms. Sensitivity is comparable to other forms of screening and diagnosing with a sensitivity of 85–95% for urethral and endocervical specimens. In addition, cultured specimens can be sent for susceptibility testing. However, isolating gonorrhea can be cumbersome. Given the polymicrobial nature of many of the sites cultured for gonorrhea, selective enriched medium with supplementation must be used. Antimicrobial agents are commonly used with the culture media to select only for gonorrhea (Bignell et al. 2006).

- One of the drawbacks of culture is the fact that a viable specimen must be collected in order to have a positive result. This is not the case for tests that rely on nucleic acid sequences. Nucleic acid hybridization or amplification tests can use nonviable specimens from samples such as urine or self-taken swabs. The sensitivity has been reported to be as high as 95% for endocervical and urethral samples. One drawback to the use of nucleic acid tests is that they do not necessarily have a viable organism to which susceptibility testing can be performed. However, as discussed below, treatment for *N. gonorrhoeae* infection typically consists of one dose of 250 mg of intramuscular ceftriaxone with 1 g of azithromycin orally. Specificity remains high in the nucleic acid tests with reports as high as 99%. Given the high sensitivity of NAATs, they are currently considered the gold standard for detection of *N. gonorrhoeae* (Bignell et al. 2006).

3.3 Sites for Testing

Many sites are at risk for infection with gonorrhea. The most common are mucosal sites, but systemic and ophthalmic sites are susceptible to infection as well. Any mucosal site associated with the common symptoms of gonorrhea should undergo testing. The appropriate test to detect gonorrhea will depend on the site the specimen is to be obtained from, the normal flora of these sites, and the indication for testing (Table 4). For example, NAATs are a highly used method of testing for many mucosal sites, such as the endocervix. However, in cases where abuse or sexual assault is of concern, tissue culture is the preferred method (CDC 2014). One of the easiest samples to obtain is patient-collected vaginal samples. These samples are ideal for patients who have symptoms but are adverse or hesitant to undergo a speculum examination. Many clinicians find this an acceptable form of testing for the pediatric and adolescent population (Schachter et al. 2005). NAATs have a high sensitivity and are an acceptable form of testing:

- Since there is still the possibility of cross-reactivity and false positives with other vaginal flora, in situations where rape or abuse is suspected, culture remains the preferred method of testing.
- Urine is another commonly used noninvasive specimen which can be used for screening and diagnostic testing. The sample should typically be obtained from the first 30 ml of voided urine. Urine samples are best tested using NAATs.
- The endocervical sample from women can be used to test for all methods. Drawback to the endocervical collection are necessity of speculum exam which sometimes deters patients and use of vaginal lubricant. Vaginal lubricant has been shown to be toxic to gonorrhea (Bignell et al. 2006) and can lead to a nonviable specimen. Urethral samples are another mucosal site which can be appropriately tested using the abovementioned tests.
- The rectum and oropharyngeal sites are unique from other mucosal sites for testing. These mucosal sites are populated by normal flora and consistent of many gram-negative rods and cocci (Todar 2012). Given the high prevalence of other bacteria which populate these sites, NAATs have a high rate of false positives. The nucleic acid composition of other bacteria can cross-react and lead to false positives. The same can be said for microscopy and gram stain. Given that these two mucosal sites are heavily populated with other flora, microscopy with gram stain is difficult secondary to

Table 4 Testing sites for gonorrhea

Testing site	Appropriate test
Endocervix	NAATs, microscopy, culture
Urethra	Microscopy, culture, NAATs[a]
Vagina	NAATs
Urine	NAATs
Rectum	Culture
Oropharynx	Culture

[a]NAATs are less sensitive for urethral specimens in asymptomatic male

the presence of other bacteria. For this reason, culture is the best way to identify *N. gonorrhoeae* infection in the rectum or oropharynx (USPTF 2014).

3.4 Treatment

N. gonorrhoeae is a highly resistant bacterium to the majority of antibiotics available. *N. gonorrhoeae* easily mutates and can easily acquire resistance to many classes of antibiotics. Given this reason, there is a theoretical benefit to treating gonorrhea with two classes of antibiotics to improve the efficacy of treatment and decrease the probability of gonorrhea acquiring resistance to current treatment. In addition, persons infected with gonorrhea are at higher risk for coinfection with chlamydia:

- For this reason, treatment with a cephalosporin and with azithromycin is the standard of care. Gonorrhea is typically treated with ceftriaxone 250 mg IM ×1 and azithromycin 1 g po ×1. This onetime dosing is favorable because it ensures patient compliance when given in the office setting. In the setting when ceftriaxone is unavailable, substitution with the cephalosporin cefixime is acceptable. However, cefixime does not achieve the same bactericidal blood levels as compared to ceftriaxone and can have decreased efficacy, especially for treatment of pharyngeal infection (CDC 2010).
- An alternative treatment with doxycycline 100 mg po BID for 7 days is available with those who are unable to tolerate azithromycin secondary to allergies or side effects (summarized in Table 5).

Test of cure is not routinely done after treatment is given except in patients who have persistent symptoms or represent with symptoms shorty after completion of treatment (Williams 2012). If a patient fails treatment with the recommended cephalosporin, culture should be performed to evaluate for antibiotic (CDC 2015a).

4 Herpes Simplex Virus Types 1 and 2

4.1 Background

The herpes simplex virus is a common viral infection found in the United States. There are two subtypes: HSV-1 and HSV-2. HSV-1 is often associated with orolabial transmission and is not considered a sexually transmitted disease. A large proportion of the United States population is infected with HSV-1. HSV-1 can be found in a proportion of the pediatric population and it can be spread by kissing. A large majority of people who are carriers of HSV-1 are asymptomatic and lesions only present at times of stress or if immunocompromised. Lesions typically consist of superficial ulcerations along the oral cavity, sometimes referred to as cold sores.

HSV-2 however is commonly the cause of genital herpes and transmitted through anogenital contact. HSV-2 is considered a sexually transmitted disease. Most HSV infections occur between ages 15 and 35. HSV-1 does not provide protection against HSV-2 but there is some protection against HSV-1 in individuals infected with HSV-2 (Eckert and Lentz 2012).

Subclinical herpes infections are common, but primary infections typically present with both systemic and local symptoms. Systemic symptoms can include fever, fatigue, and malaise. These symptoms are reported in 60–80% of primary herpes infections (Eckert and Lentz 2012). Local symptoms of the infected tissue include paresthesia of the surrounding skin, severe pain, inguinal lymphadenopathy, appearance of multiple vesicles, superficial ulcers, and pain. Severe symptoms typically last 10–14 days; however, it may take up to 6 weeks for lesions to heal. Since

Table 5 Treatment of gonorrhea

Antibiotic regimen	
Ceftriaxone 250 mg IM × 1 + Azithromycin 1 g po ×1[a]	Preferred regimen
Cefixime 400 mg po × 1 + azithromycin 1 g po ×1[a]	If ceftriaxone unavailable
	TOC should be performed in 1 week
Azithromycin 2 g po × 1	If patient has severe allergy to cephalosporin

2010 CDC STD treatment guidelines
[a]Doxycycline 100 mg po BID ×7 days is an acceptable alternative to azithromycin in patients who are unable to tolerate azithromycin

the ulceration is typically superficial, the lesions generally heal without evidence of scarring. During the primary infection, viral cultures yield a positive result 80% of the time (Eckert and Lentz 2012).

Recurrence is common in HSV infections and frequency is related to serotype and severity of the initial infection. Those with HSV-1 have a 50–60% risk of recurrence within the first 12 months after the initial infection, whereas those with HSV-2 typically have an 80% risk of recurrence within the first 12 months. If the initial presentation was severe, recurrence is typically twice as often. Culturing of recurrent herpes lesion only yields a positive result in 40% of cases (Eckert and Lentz 2012).

4.2 Testing for HSV-1 and HSV-2

There are several methods available for testing for infections with herpes simplex virus. Some rely on culturing of the virus, often referred to as direct testing. Others rely on identification of type-specific antibodies in the patient's blood. This second form of testing is commonly referred to as type specific or indirect testing (Singh et al. 2005).

1. Direct testing includes viral culture, Tzanck smears, DFAs, PCR, and rarely electron microscopy. Direct testing is an appropriate method of testing for patients who present with acute ulcerative lesions and are seeking diagnosis and treatment of their active lesions. One of the challenges of direct testing is the variability of sensitivity among these tests. Sensitivity is the highest for direct testing at the time of onset of the lesions. As the acute lesions begin to heal, the presence and ability to successfully collect viable virus decreases rapidly. Since direct testing relies on collecting viral specimens from the acute lesion, the sensitivity for direct testing falls drastically as the lesions begin to heal (Singh et al. 2005). A negative test does not necessarily mean that the patient is not infected with herpes, especially in a nonacute or asymptomatic patient. Since asymptomatic patients typically have intermittent viral shedding, direct testing is not the test of choice for asymptomatic patients given the very low sensitivity in this clinical scenario.
   - Viral culture has long been the gold standard for the diagnosis of HSV lesions. Specificity is recorded at 100%. Sensitivity however is variable. With time, the HSV lesions will begin to heal, as the lesions heal, the sensitivity of viral culture sharply falls. Once crusting is demonstrated around the HSV lesion ulcers, the sensitivity markedly lower than for acute lesions. Sensitivity has been reported around 75% for primary lesions and 50% for recurrent lesions (Singh et al. 2005).
   - Tzanck smears have been used to detect HSV infections. They rely on the identification of cytopathic changes in genital epithelial cells. Infected cells typically will be enlarged with multinucleated cells with clear inclusions. Typically, the Tzanck smear is prepared with the Wright-Giemsa stain and examined under the microscope. The Tzanck smear cannot differentiate between HSV-1 and HSV-2, and the test can be positive with the presence of the varicella zoster virus. The Tzanck smear does not replace other diagnostic testing, but rather serves as a way to aid in immediate diagnosis when other testing modalities are unavailable (Singh et al. 2005).

- Herpes PCR is considered the test of choice for diagnosing HSV infections of the central nervous system such as meningitis or encephalitis. In the setting of HSV central nervous system infections, PCR has greater sensitivity and detection than viral culture (Singh et al. 2005). In addition, since PCR relies on the amplification of segments of viral DNA rather than the culture of viable virus, PCR will yield a positive result several days after lesions no longer contain the infectious virus (Singh et al. 2005). HSV PCR is replacing viral culture as the gold standard for the diagnosis of genital herpes in women with active mucocutaneous lesions (Strick and Wald 2006).

2. Serologic tests indirectly test for HSV infection by detecting circulating antibodies produced by the host's immune system. This has the advantage over direct testing, because serologic testing can detect infected persons who are asymptomatic and would otherwise produce a false-negative result. Indirect serologic type-specific testing is useful in situations where viral culture/PCR returns negative, in patients with recurrent herpes, or when testing asymptomatic partners for HSV (CDC 2015a). Western blot detecting of HSV antibodies is the most specific test available to detect recurrent HSV lesions. It is currently considered the gold standard for detecting antibodies to HSV. One of the advantages of Western blot testing is that it can discriminate between types of HSV, HSV-1 and HSV-2. Western blot however is not widely available, very labor intensive, and time consuming.
   - Enzyme-linked immunosorbent assays (ELISA) are also commercially available to test for type-specific antibodies in patients' blood to HSV. ELISA technologies have been reported to have sensitivities from 97% to 100% and specificity as high as 98% in the detection of HSV-1 and HSV-2. Several of the current commercial ELISA tests for HSV-2 can yield a false positive at low values. In situations where a false-positive result is of consideration, Western blot should be performed to verify results (CDC 2015a). ELISA testing is available as point of care testing from capillary blood samples that can be done in the clinic.
     - Since type-specific testing can differentiate between HSV-1 and HSV-2, it is important to counsel patients on the significance of the result. HSV-1 can be acquired through orolabial transmission or through anogenital contact. The positive result of HSV-1 does not necessarily imply a sexually transmitted disease. However, HSV-2 is commonly transmitted through anogenital contact and is considered a sexually transmitted disease. Those who test positive for HSV-2 should be informed of their diagnosis, counseled on safe sex practices and risk of transmission to partners, and offered screening for other sexually transmitted diseases. It is recommended that patients who test positive for HSV-2 also be offered screening for HIV (CDC 2015a).

4.3 Treatment

Treatment for herpes infection can be divided into two separate arms. The first arm is aimed at treating the acute outbreak, either primary or recurrent. The second arm is aimed at preventing future outbreaks and decreasing the risk of transmission to a noninfected partner. Even without active lesions, there is asymptomatic viral shedding which puts partners at risk for transmission:

- The primary outbreak is typically treated with acyclovir 400 mg orally TID or 200 mg 5× a day for 7–10 days.
- Valacyclovir 1 g BID for 7–10 days or famciclovirr 250 mg TID ×7–10 days can also be used (Table 6).
- For recurrent outbreaks, treatment should be initiated during the prodromal phase or within the first 24 h of active outbreaks (Table 7). There are many treatment options available but typically acyclovir 400 mg po BID and 800 mg BID for 5 days are used.

Table 6 Primary treatment of HSV outbreak

Regimen	
Acyclovir 400 mg po TID ×7–10 days	Primary outbreak
Acyclovir 200 mg po five times daily ×7–10 days	Primary outbreak
Valacyclovir 1 g po BID ×7–10 days	Primary outbreak
Famciclovir 250 mg po TID 7–10 days	Primary outbreak

Table 7 Recurrent HSV outbreak Treatment

Regimen	Recurrent outbreak therapy
Acyclovir 400 mg po TID ×5 days	
Acyclovir 800 mg po BID ×5 days	
Acyclovir 800 mg po TID ×2 days	
Valacyclovir 500 mg po BID ×3 days	
Valacyclovir 1 g po ×5 days	
Famciclovir 125 mg po BID ×5 days	
Famciclovir 1 g po BID ×1 day	

- Other regimens exist as well. Table 8 lists treatment options available for suppressive therapy to reduce viral shedding, transmission to partners, and future outbreaks.

Table 8 Suppressive HSV therapy

Regimen	Suppressive therapy
Acyclovir 400 mg po BID	
Valacyclovir 500 mg po daily	
Valacyclovir 1 g po daily	
Famiciclovir 250 mg po BID	

5 Human Papillomavirus (HPV)

5.1 Background

Human papillomavirus (HPV) is a double-stranded DNA virus from the papillomavirus family that commonly infects the transitional zone in the cervix. HPV infection is the number one sexually transmitted disease in the United States with an estimate of more than 79 million persons infected with the virus (CDC 2013, 2015b). The majority of HPV infections will resolve on their own after 2 years. However, some infections are persistent and can significantly increase the risk for cervical and other cancers.

High-risk HPV plays an important role in cell cycle dysregulation. They commonly affect the oncoproteins E6 and E7 (Oh et al. 2005). When expressed, E6 oncoprotein binds to the P53 tumor suppressor gene and leads to its degradation. In a similar method, E7 binds to the RB tumor suppressor gene and inhibits its regulatory function. Seventy to 80% of cervical cancer is secondary to squamous cell carcinoma of the cervix. Studies have shown that nearly 100% of squamous cell carcinoma of the cervix is attributable to high-risk HPV (Saslow et al. 2012). HPV subtypes 16 and 18 are the most commonly encountered high-risk HPV subtypes. High-risk HPV refers to their oncogenic properties. Nearly 55–60% of cervical cancer appear to be caused by HPV 16 (Saslow et al. 2012).

It is well known that HPV is transmitted through sexual contact. Given that HPV is a virus, a healthy host's immune system will try to rid the body of the virus. For this reason, the majority of HPV infections are transient, lasting only 1–2 years. During the time of infection, it is possible to spread HPV to another sexual contact, thus, leading to the high prevalence of HPV in the population. If the HPV infection is not cleared from the body and persists, there is increased risk of developing cervical cancer or a precancerous lesion (Saslow et al. 2012).

The progression from normal cervical cytology to cervical cancer has been well studied. It is understood that the development of cervical cancer consists of precancerous lesions termed cervical intraepithelial neoplasia I, II, and III (CIN I, CIN II, CIN III). The progression of cervical cancer generally proceeds through each of these precancerous stages before malignant cells are formed. The fundamentals of cervical cancer screening are based on identifying abnormal cytology on the pap smear prior to the

development of cervical cancer. With the advent of HPV testing in conjunction with cervical cytology testing, it is possible to identify those at high risk for development of cervical cancer and need shortened interval testing between cytologic examinations.

Currently, HPV screening has two primary uses. The first is in the setting of an equivocal cytology test (ASC-US). The presence of HPV will dictate the interval of screening and if further evaluation is necessary. In a patient who has a negative pap based on cytology, the presence of high-risk HPV will dictate whether the patient will need immediate colposcopy vs. contesting in 1 year. The same can be said for when a pap smear shows a low-grade squamous intraepithelial lesion (LSIL). If the patient had been tested for HPV and the result is negative, co-testing in one tear is acceptable to evaluate for clearance of the abnormal cytology. However, in the setting when HPV status is unknown or the patient tests positive for high-risk HPV, then the patient needs further work-up with colposcopy (Saslow et al. 2012).

The second major use of HPV is for co-testing with cytology in patient's 30 years of age or older. Cytology with HPV testing can increase the interval between pap smears from 3 to 5 years (Saslow et al. 2012). For example, persons with a persistent HPV 16 infection for 1–2 years have a 20–30% risk of developing CIN III over the course of 5 years. If CIN III goes untreated, there is a 30% probability that it will develop into invasive cervical cancer over 30 years. In contrast, the risk of treated CIN III progressing to invasive cervical cancer over 30 years is quoted to be 1% (McCredie et al. 2008). Given that the median age of first intercourse in the United States is around 17 years of age and the high prevalence of HPV in the general population, one's risk of becoming infected with a high-risk HPV in their earlier years is significant:

- HPV testing in the setting of cytology allows for increased detection of high-risk patients, safely allows an increase in the interval between cytologic examination in low-risk individuals, and directs triaging of equivocal cytology results. In a reassuring study examining the change in lifetime risk for a 40-year-old woman undergoing cytology every 3 years versus contesting every 5 years showed a lifetime cervical cancer risk of 0.69% and 0.61%, respectively (Stout et al. 2008). Thus, showing the benefits is contesting.

5.2 Screening and Diagnosis

There are various methods for detecting HPV including cytology, hybrid capture, invader chemistry, PCR, and cytology. Even though various tests exist for detecting HPV, only two are FDA approved at this time (Hybrid Capture II and Cervista NPV):

- In 2014, the FDA approved the use of a HPV DNA test [cobas] for reflex or co-testing and primary screening (detects HPV types 16 or 18 and gives pooled results for 12 additional high-risk HPVs) as first-line primary screening test for use alone for women age 25 and older.
- The Hybrid Capture II relies on signal amplification using RNA probes directed against the DNA sequence of 13 high-risk HPV types (Nishino et al. 2011). The RNA will bind to the DNA from the HPV creating DNA-RNA hybrids which can be bound to a testing plate. This bound compound is then reacted with various substrates to emit light. At a given intensity, the test will be considered positive. Meta-analysis of the Hybrid Capture II sensitivities ranged from 92.5% to 95.6% (Nishino et al. 2011).
- The Cervista HPV HR and HPV 16/18 are signal amplification tests that rely on invader chemistry technology to detect the presence of HPV in cervical samples. The Cervista HPV HR was the first FDA approved test for detection of HPV in women. It can be used with specified cervical cytology collecting instruments such as the cervix brush and pipette and for use with the Thin Prep Pap Test

PreservCyt Solution. The sensitivity for the Cervista when used according to FDA specification ranges from 92.8% to 100% (Nishino et al. 2011).

- Cervical cytology can detect morphologic effects of HPV– koilocytosis, nuclear hyperchromsia/enlargement, and cytoplasmic cavitation – but cannot differentiate high-risk from low-risk HPV.

5.3 Treatment

Currently there is no treatment for the HPV virus itself. There is only treatment for the HPV-related complications (CDC 2013, 2015b).

6 Conclusion

There is a high prevalence of sexually transmitted disease in the United States of America. While each sexually transmitted diseases is associated with its own unique signs and symptoms, they are often asymptomatic. Untreated sexually transmitted diseases can cause sequel such as infertility, hospitalization, cancer, sepsis, and death. It is the clinicians responsibility to know the indications for screening or testing patients for sexually transmitted disease. With today's technology, there are vast arrays of tests available to the clinician for the screening and diagnosing of sexually transmitted diseases. Each test has its own unique indications and may show superiority based on the pathogen and site being tested. It is imperative that the clinician is familiar with the tests available for diagnosis and the indications for each.

Proper screening and diagnosing of sexually transmitted diseases will lead to earlier detection, a reduction in time to treatment, and a reduction of overall complications from undiagnosed and untreated sexually transmitted infections.

7 Cross-References

- ▶ Benign Vulvar and Vaginal Pathology
- ▶ Common Problems in Adolescent Medicine
- ▶ Current Recommendations in Gynecology: Preventive Health Care, Screening, Immunizations
- ▶ Diagnosis and Treatment of Urinary Tract Infections
- ▶ Diagnosis and Treatment of Vulvovaginitis
- ▶ Fertility Sparing Treatment for Early-Stage Cervical Cancer
- ▶ Gynecologic History and Examination of the Patient
- ▶ Management of Cervical Dysplasia
- ▶ Management of Chronic Recurrent Vulvovaginitis
- ▶ Management of Early-Stage and Locally-Advanced Cervical Cancer
- ▶ Management of Intraepithelial Lesions of the Cervix
- ▶ Management of Metastataic and Recurrent Cervical Cancer
- ▶ Management of the Symptoms of Perimenopause
- ▶ Pelvic Inflammatory Disease and Other Upper Genital Infections
- ▶ Sexually Transmitted Diseases: Diagnosis and Work-Up (GC, Chlamydia, Herpes HPV)

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Diagnosis and Treatment of Vulvovaginitis

Mya Rose Zapata

Abstract

Vulvovaginitis symptoms are common and are the most frequent reason for visits to the obstetrician gynecologist. Vulvovaginitis symptoms are prevalent in a large range of age groups, and they can have a significant impact on women's lives. The most common cause of vaginitis is bacterial vaginosis and the other two common causes are candida vaginitis and trichomoniasis. Together theses account for over 90 % of all vaginitis diagnosis. Self-diagnosis is common but often inaccurate. Vaginitis is associated with increased risk of acquiring a sexually transmitted disease or other female genital tract infections including human immunodeficiency virus (HIV). Theses concurrent conditions may result in infection of the upper genital tract and can lead to infertility as well as adverse reproductive and medical outcomes in pregnant and non pregnant women. Evaluation consists of a detailed focused history, physical exam, and appropriate diagnostic testing. Empiric therapy based on history and physical examination alone should be avoided because of frequent misdiagnosis and inappropriate therapy. Treatment should be chosen based on diagnostic findings and may be guided by cost, patient convenience and patient preference and directed to treat the most common causes such as bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. A discussion on proper vaginal hygiene including gentle cleaning and drying the vulvar area may be useful.

Keywords

Vaginitis • Vulvovaginal infection • Yeast vaginitis

Contents

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1 Introduction

Vulvovaginitis symptoms are very common in women, making vulvovaginitis one of the most frequent reasons for patient visits to the obstetrician gynecologist. The term vulvovaginitis is used for a range of disorders of the vulva and vagina and commonly includes symptoms such as vulvar or vaginal burning, irritation, pruritus, odor, and/or abnormal discharge. These symptoms are prevalent in a large range of age groups and frequently lead to self-diagnosis and therapy (American College of Obstetricians and Gynecologists 2015).

> Vulvovaginitis has a broad differential diagnosis and successful treatment and symptom resolution often relies on an accurate diagnosis and appropriate treatment as well as patient education.

Causes of vulvovaginitis symptoms may be related to shifts in the vaginal flora, local inflammation, infection, or hormonal changes to vaginal epithelium. Although this may seem like a small issue to some, symptoms can significantly impact women's daily lives leading to severe discomfort, pain, loss of work or school days, cost of treatments, psychological stress, change in self-image, and sexual functioning.

The most common causes of vaginitis in symptomatic women are bacterial vaginosis (40–45 %), vaginal candidiasis (20–25 %), and trichomoniasis (15–20 %). These disorders together account for over 90 % of vaginal infections (Sobel 1999). Up to 75 % of women will have at least one episode of vaginal candidiasis in their lifetime (Sobel 1997). Vulvovaginitis can be associated with sexually transmitted diseases and other infections of the female genital tract, including human immunodeficiency virus (HIV) (Sewankambo et al. 1997; Taha et al. 1998). It has also been found to have adverse reproductive outcomes in pregnant and nonpregnant women depending on the etiology.

Other common causes of these symptoms include vaginal atrophy/atrophic vaginitis, cervicitis, foreign body, irritants and allergens, and several rarer entities, including some systemic medical disorders.

2 Pathogenesis

Estrogen status plays a crucial role in determining the normal state of the vagina. In the prepubertal and postmenopausal states, the nonkeratinized stratified squamous epithelium of the vagina is thinned, and the pH of the vagina is usually elevated (pH 4.7 or greater). The typical vaginal flora demonstrates a broad variety of organisms, including typical skin and fecal flora. During the reproductive years, the presence of estrogen causes the vaginal epithelium to become rich in glycogen. Lactobacilli convert glycogen from sloughed cells into lactic acid, creating an acidic vaginal environment (pH 4.0–4.5). This acidity helps maintain the normal vaginal flora and inhibits growth of various pathogenic organisms. However, even in asymptomatic women of reproductive age, the normal vaginal flora of women remain heterogeneous, and other components of the vaginal flora, such as Gardnerella vaginalis, *Escherichia coli*, group B streptococci (GBS), genital mycoplasmalates, and *Candida albicans*, are commonly found. Disruption of the normal ecosystem can lead to conditions favorable for overgrowth of certain organisms and development of vaginitis. Some of the potentially disruptive factors include phase of the menstrual cycle, sexual activity, contraceptive choice, pregnancy, foreign bodies, estrogen status, sexually transmitted diseases, other medical comorbidities, use of

antibiotics, stress, and use of various hygienic products (Sobel 2016a).

3 Etiologies

3.1 Candidal Vulvovaginitis

Candidal vulvovaginitis refers to a disorder characterized by signs and symptoms of vulvovaginal inflammation in the presence of Candida species. It accounts for approximately one-third of vaginitis cases and is the second most common cause of vaginitis symptoms (Workowski and Bolan 2015). It is generally not considered an opportunistic infection, and it is not considered a sexually transmitted disease.

Candida albicans is responsible for 80–92 %of episodes of vulvovaginal candidiasis (Odds 1988), and *C. glabrata* accounts for almost all the remainder (Sobel 2007). Some investigators have reported an increasing frequency of non-albicans species, particularly *C. glabrata* (Horowitz et al. 1992 and Vermitsky et al. 2008), possibly due to widespread use of over-the-counter antifungals, long-term use of suppressive azoles, and the use of short courses of antifungal drugs.

All Candida species produce similar vulvovaginal symptoms, although the severity of symptoms is milder with *C. glabrata* and *C. parapsilosis*. Candida organisms probably access the vagina via migration from the rectum across the perineal area (Bertholf and Stafford 1983); cultures of the gastrointestinal tract and vagina often show identical Candida species. Less commonly, the source of infection is sexual or relapse from a vaginal reservoir.

Symptomatic disease is associated with an overgrowth of the organism and penetration of superficial epithelial cells (Sobel et al. 1998). The mechanism by which Candida species transform from asymptomatic colonization to an invasive symptomatic form causing symptomatic vulvovaginitis is complex, involving host inflammatory responses and yeast virulence factors.

3.2 Bacterial Vaginosis

Bacterial vaginosis (BV) represents a complex change in the vaginal flora characterized by a reduced concentration of lactobacilli and an increase in concentration of other organisms, especially anaerobic gram negative rods (Sobel 2016b; Ling et al. 2010). BV is typically a polymicrobial infection, and organisms that are found with greater frequency and numbers in women with BV include *Gardnerella vaginalis*, *Prevotella* species, *Porphyromonas* species, *Bacteroides* species, *Peptostreptococcus* species, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Fusobacterium* species, *Atopobium vaginae*, and *Mobiluncus* species (Hill 1993; Lamont et al. 2011). Because these organisms are part of the normal flora, the mere presence of these organisms, especially *G. vaginalis*, on a culture does not mean that the patient has bacterial vaginosis. The mechanism by which the imbalance occurs in the vaginal flora and the role of sexual activity in the pathogenesis of BV are not clear.

Lactobacilli are important in preventing overgrowth of the anaerobes normally present in the vaginal flora. With the loss of lactobacilli, pH rises and massive overgrowth of vaginal anaerobes occurs. These anaerobes produce large amounts of proteolytic carboxylase enzymes that break down vaginal peptides into a variety of amines that are volatile and malodorous and associated with increased vaginal transudation and squamous epithelial cell exfoliation. Thus, patients with BV, when symptomatic, may complain of an abnormal vaginal discharge and a fishy odor.

> In nonpregnant women, BV has been associated with infections of the female reproductive tract, including pelvic inflammatory disease (PID), post-procedural gynecologic infections, and acquisition of HIV and herpes simplex virus (HSV)-2 infections (Beigi 2004).

In addition to sexual and infectious risk factors, studies indicate that douching and cigarette smoking are risk factors for acquisition of BV

among sexually active women (Hillier et al. 1995; Sobel 2016c). Although some degree of genetic susceptibility to BV is hypothesized, a specific gene polymorphism has not been established (Carey et al. 2000).

3.3 Vaginal Trichomoniasis

Vaginal trichomoniasis is a common sexually transmitted disease with an estimated annual incidence of 7.4 million cases in the United States (Weinstock et al. 2004). *Trichomonas vaginalis* is the flagellated protozoan organism responsible for trichomoniasis, and it principally infects the squamous epithelium in the urogenital tract, including the vagina, urethra, and paraurethral glands (Sobel 2016e). Other less common sites include the cervix, bladder, and Bartholin glands. Humans are the only natural host for this organism. Trichomoniasis is virtually always sexually transmitted. Although survival on fomites, such as clothing or bedding, has been reported, fomites have no proven role in transmission. Women can acquire the disease from other women, but men do not usually transmit the infection to other men. The exact incubation period is unknown; however, the estimated incubation period is 4–28 days (Sobel 2016e).

Symptomatic women with trichomoniasis may have an abnormal discharge, itching, burning, or postcoital bleeding. Vaginal pH is typically elevated (pH greater than 4.5), However, diagnosis in clinical settings relies on visualization of motile trichomonads on saline microscopy. A wet mount has a sensitivity of 55–60 % in diagnosing trichomoniasis (Krieger et al. 1988). Trichomonas culture techniques are associated with greater than 90 % sensitivity but are impractical because a special media is required and few laboratories are equipped (Fouts and Kraus 1980). Nucleic acid amplification tests (NAATs) for trichomonal DNA are sensitive and specific. A point-of-care test for trichomonas antigens, the OSOM Trichomonas rapid test, has a sensitivity of 88.3 % and specificity of 98.8 % (Baron et al. 2013) compared with culture. OSOM is available for office use and results are available in 10 min. This test may be a valuable diagnostic tool, particularly in settings with a high prevalence of trichomoniasis and where microscopy or culture is not available.

3.4 Other Etiologies of Vulvovaginal Symptoms

Although vulvovaginal symptoms are most commonly caused by candidiasis, bacterial vaginosis, and trichomoniasis, other causes may include atrophic vaginitis, vulvar diseases, and other rarer forms of vaginitis.

3.4.1 Atrophic Vaginitis

Atrophic vaginitis (also referred to as vulvovaginal atrophy, vaginal atrophy, or urogenital atrophy) results from decreased systemic estrogen and is often associated with vulvovaginal complaints, such as dryness, burning, and dyspareunia in menopausal women. Urinary frequency and recurrent bladder infections may also occur.

The drop in estrogen concentration due to menopause or other hypoestrogenic state is responsible for many of the changes seen with vulvovaginal atrophy (Bachman and Santen 2016a). These changes usually develop gradually over years and, for many women, persist unless they are treated. The top layer of superficial epithelial cells thins and is sometimes completely lacking in women with severe atrophy. There is loss of elasticity of the vaginal epithelium and increase in subepithelial connective tissue. The rugae are lost resulting in a smooth appearing epithelium. The vaginal canal often shortens and narrows and overall is less distensible. Total vaginal secretions are reduced, and the low glycogen content of the thinned epithelium leads to reduction in lactic acid production by lactobacilli, and subsequently vaginal pH is increased (pH $\geq$5). Thinning of the vaginal epithelium makes it more susceptible to trauma, leading to bleeding, petechiae, and ulceration with any pressure. Thinning also exposes the underlying connective tissue, which is more vulnerable to inflammation or infection.

The changes in the vaginal environment encourage the overgrowth of nonacidophilic coliforms and the disappearance of lactobacilli. This predisposes affected women to infection by local skin and rectal flora (e.g., streptococci, staphylococci, coliforms, diphtheroids), as well as Candida species, bacterial vaginosis, and *Trichomonas* species (Pandit and Ouslander 1997).

3.4.2 Desquamative Inflammatory Vaginitis

Desquamative inflammatory vaginitis is thought by most to be an inflammatory vaginitis of noninfectious etiology, with secondary bacterial microbiota disruption (Sobel 2016d). No consistent microbiologic pathogen has been identified except for the near absence of lactobacilli in almost all affected women (Sobel et al. 2011). The presentation is characterized by vaginal/introital pain, dyspareunia, and/or burning with diffuse exudative vaginitis and epithelial cell exfoliation, resulting in profuse vaginal discharge ranging in color from yellow to gray or green (Reichman and Sobel 2014). The specific etiology of the process is poorly understood.

3.4.3 Vulvovaginal Dermatitis

One-third to one-half of vulvar complaints stem from vulvar dermatitis. It can develop in isolation or may occur as part of dermatitis in other areas of the body such as eczema or psoriasis. Women with vulvar dermatitis often experience chronic irritation or pruritus, which cause them to persistently rub and scratch the vulva causing histologic changes in the dermis, called lichen simplex chronicus (Johnson et al. 2016).

Compared with other body regions, vulvar skin is particularly vulnerable to irritants and allergens and is more permeable than exposed skin to occlusion, hydration, and susceptibility to friction. As an example, commonly used preservatives may induce a greater response after application to normal vulvar skin than when applied to the skin of the forearm (Farage and Maibach 2004). A new allergen is most likely to induce a reaction; however, patients may also react to products that they have used for months or years. A delayed hypersensitivity (type IV) reaction may take from 12 to 72 h to develop, is usually pruritic, and often lasts for several weeks. In acute cases, an exposure occurring up to 2 weeks prior to the resulting dermatitis can often be identified. In chronic cases, the dermatitis may have been present for months or years; identifying the offending trigger in these patients can be difficult. Chronic wetness of the vulva due to a variety of etiologies is associated with skin irritation and dermatitis.

In acute vulvar dermatitis, the skin displays mild to severe erythema of varying extent with some scaling in dry areas. Fissures may be present along the labial folds. Excoriations from scratching are common and can be complicated by secondary infection with yeast or bacteria (e.g., *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Escherichia coli*). Although crusts and scales are commonly observed with dermatitis elsewhere on the body, these signs are often not present in the moist areas of the vulva.

The most common symptom of vulvar dermatitis is pruritus, which can be intense and nocturnal. Other symptoms include burning, stinging, or rawness. Symptoms may be exacerbated by heat, sweat, stress, or menstruation. Self-medication and excessive washing of the vulva by women fearful of a lack of cleanliness often aggravate the dermatitis. Repeated cycles of intense itching and scratching result in the thickening of the vulvar epidermis and accentuation of the normal skin marking, called lichen simplex chronicus (Lynch 2004). Labial skin folds appear greatly exaggerated, often edematous, and pubic hair can be broken or sparse (Marren 1996). Other changes that can be seen include hypopigmentation or hyperpigmentation and hyperkeratosis (Johnson et al. 2016).

4 Evaluation

Vaginitis symptoms are often nonspecific; thus, it is valuable to document the etiology of vaginitis using diagnostic laboratory testing before initiating therapy. Empiric therapy based on history and physical examination alone should be avoided because of frequent misdiagnosis and

inappropriate therapy. Diagnostic testing enables targeted treatment, increases therapeutic compliance, and increases the likelihood of partner notification when indicated (Workowski and Bolan 2015). However, 25–40 % of patients with genital symptoms do not have a specific cause identified after initial diagnostic testing (Baron et al. 2013). These women tend to have a noninfectious etiology of symptoms.

The three main steps in the evaluation of women with symptoms of vaginitis are:

- Obtain a history and perform a physical examination
- Test for bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis since these disorders account for over 90 % of vaginitis in premenopausal women and can be diagnosed by pH testing, microscopy, culture, rapid antigen, and nucleic acid amplification tests
- Depending on risk factors test for other infections of the genital tract such as *Neisseria gonorrheae* and *Chlamydia trachomatis*

If this evaluation does not lead to a diagnosis, then evaluation for less common and rare cases of vaginitis may be appropriate. (Sobel 2016a).

5 History

Vulvovaginitis has a very broad differential diagnosis. Making an accurate diagnosis requires a detailed focused history covering the spectrum of vaginal symptoms including changes in discharge, vaginal odor, itching, irritation, burning, swelling, dyspareunia, and dysuria. Questions about the location of symptoms (vulva, vagina, anus), duration, the relation to the menstrual cycle, the response to prior treatment including self-treatment and douching, other aggravating or mitigating factors, and a sexual history can provide important insights into the likely etiology.

Women with vulvovaginitis typically present with one or more of the following symptoms:

1. Abnormal vaginal discharge: this may be defined by women as a change in color, odor, consistency/viscosity, or volume of their typical vaginal discharge.
2. Pruritus: women may describe pruritus of the external genitalia, internal vaginal walls, or nonspecific sense of pruritus in the genital area that can occasionally be hard for women to localize when describing.
3. Burning: women may describe a burning sensation of the vulvar epithelium or vaginal mucosa, sometimes when provoked by touch (i.e., wiping with toilet paper, touch, intercourse, tampon, clothing), sometimes constant and unprovoked.
4. Irritation: often described as a general feeling of "soreness" or "raw" feeling of the genital area or sensitivity of vulvar epithelium or vaginal mucosa with or without "swelling."
5. Erythema: erythema may be present on external vulvar epithelium and/or erythema of vaginal mucosa.
6. Dyspareunia: women may describe introital dyspareunia that starts from initiation of sexual activity or may describe introital dyspareunia that develops after a period of comfortable sexual relations, tampon use, or speculum examinations.
7. Spotting: this may be described as inter menstrual spotting, postcoital spotting or postmenopausal spotting.
8. Dysuria: pain with urination that is generalized or involves the external genitalia from contact with acidic urine.

Vaginal discharge is often the presenting chief complaint. This can be difficult to distinguish from normal vaginal discharge on evaluation. Occasionally other symptoms may make a woman more aware of her genital area and cause increased attention to her vaginal discharge that she otherwise was not specifically aware of. This increased awareness can occasionally cause individuals to be hypersensitive to their discharge feeling that any discharge is abnormal.

Normal vaginal discharge in reproductive aged women typically consists of 1–4 mL fluid (per 24 h) that is white or transparent, clear or slightly

cloudy, thick or thin, and mostly odorless. This physiologic discharge is formed by mucoid endocervical secretions, sloughing epithelial cells, normal vaginal flora, and normal vaginal transudate. The discharge may become more noticeable at various times, such as at mid-menstrual cycle near ovulation, during pregnancy or during use of estrogen-progestin contraceptives, and is often called "physiological leukorrhea." Diet, sexual activity, medication, and stress can affect the volume and character of normal vaginal discharge. Although normal discharge may be yellowish and slightly malodorous and accompanied by mild irritation symptoms, it is not accompanied by pruritus, pain, burning or significant irritation, erythema, local erosions, or cervical or vaginal friability. The absence of these signs and symptoms is what distinguishes it from discharge related to a pathological vaginitis or cervicitis (Sobel 2016a).

6 Physical Exam

- A thorough external evaluation of the vulva should be performed since many patients have vulvar manifestations of disease. The exam is focused on the degree of vulvovaginal inflammation, characteristics and amount of visible vaginal discharge, odor, and the presence of any abnormal lesions or possible foreign bodies. Clinicians must keep in mind that patient self-treatment with over the counter medications may alter the appearance of the vulva, vaginal tissue, and discharge.

  The vulvar epithelium usually appears normal in bacterial vaginosis, the most common cause of vaginitis. The presence of edema, erythema, or fissures may suggest candidiasis, trichomoniasis, or dermatitis. Atrophic changes such as pale vaginal mucosa and loss of rugae may suggest a hypoestrogenic state and suggests the possibility of atrophic vaginitis. Changes in vulvar architecture may be caused by severe atrophy, chronic dermatitis, or a more uncommon chronic inflammatory process such as erosive lichen planus, lichen sclerosis, or mucous membrane pemphigoid, rather than vaginitis.
- Speculum exam is indicated as it may reveal a lesion contributing to the patient's symptoms:
  - A foreign body (such as a tampon, condom, sex toy, contraceptive ring, or pessary) is easily detected with a speculum exam and is often associated with abnormal vaginal discharge, irregular bleeding or spotting, and/or an abnormal or unpleasant odor due to inflammation and secondary infection. Removal of the foreign body is generally adequate treatment. The vaginal ecosystem will typically re-equilibrate and antibiotics are rarely needed.
  - Vaginal warts are skin colored or pink and range from smooth flattened papules to a verrucous, papilliform appearance. When they are numerous or large, they can be associated with abnormal vaginal discharge, pruritus, bleeding, burning, tenderness, and pain.
  - Granulation tissue or surgical site infection can cause vaginal discharge after hysterectomy, operative procedures on cervix or uterus, or after childbirth
  - Necrotic or inflammatory changes associated with malignancy in the lower up upper genital tract can result in vaginal discharge; spotting is more common in this setting than in infectious vaginitis.
  - The presence of multifocal, rounded macular erythematous lesions like a spotted rash or bruise, purulent discharge, and tenderness suggests erosive vulvovaginitis which can be caused by trichomoniasis or one of several noninfectious inflammatory etiologies.
  - The characteristics of the vaginal discharge may help distinguish the type of infection, if present. Trichomoniasis is typically associated with a greenish-yellow purulent discharge; candidiasis with a thick, white, adherent, "cottage cheese-like" discharge; and bacterial vaginosis with a thin, homogenous, "fishy smelling" gray discharge. Inflammation and/or necrosis related to malignancy of the lower or upper genital

tract can result in watery, mucoid, purulent, an/or bloody vaginal discharge and warrants further diagnostic workup. However, the appearance of the discharge alone is unreliable and should not form the basis of diagnosis.
  - Cervical inflammation with a normal vagina is suggestive of cervicitis, rather than vaginitis. The cervix in women with cervicitis is usually erythematous and friable, with mucopurulent discharge, which is sometimes caused by *Neisseria gonorrheae* or *C. trachomatis*. This may as an abnormal yellow discharge. A normal cervical ectropion must be distinguished from cervical erythema, as this is a common finding and is the normal physiologic presence of endocervical glandular tissue on the exocervix. A prominent ectropion is more common in women taking oral estrogen containing contraceptive pills and during pregnancy. A prominent ectropion may increase the volume of vaginal discharge.
  - Vesicovaginal and rectovaginal fistulas must be considered as a source of chronic vaginal discharge but are rare and are hard to detect. Patents at risk for this are patients who are post-hysterectomy and postsurgery for prolapse or have a history of inflammatory bowel disease or radiation to the pelvis.
- Bimanual exam may reveal pelvic or cervical motion tenderness suggestive of pelvic inflammatory disease (PID) as well as pelvic muscle spasm and tenderness which may indicate pelvic muscle dysfunction and pain (Sobel 2016a).

7 Diagnostic Studies

During speculum examination, samples should be obtained for vaginal pH, amine "whiff" test, and saline wet mount and 10 % potassium hydroxide (KOH) microscopy.

- Vaginal pH: measurement of the vaginal pH is the most important finding that drives the diagnostic process and should always be determined (Sobel 2016a). The pH and amine testing can be performed either through direct measurement or by colorimetric testing. It is important that the swab for pH evaluations be obtained from the mid-portion of the vaginal sidewall to avoid false elevations in pH results caused by cervical mucus, blood, semen, or other substances. A pH test stick or pH paper is applied for a few seconds to the vaginal sidewall. Alternatively, the vaginal sidewall can be swabbed with a dry swab and then the swab rolled onto a pH paper. The pH specimen is only stable for about 2–5 min at room temperature after collection. The swab should not be premoistened as the moistening liquid can affect the pH. An elevated pH in a premenopausal woman suggests infections such as bacterial vaginosis (pH >4.5) or trichomoniasis (pH 5–6) and helps exclude Candida vulvovaginitis. If a large amount of blood is present and contamination of the specimen is unavoidable, then pH will not be diagnostic as blood will typically raise the specimen pH.

> The pH of the normal vaginal secretions of premenopausal women is typically 4.0–4.5.

- Microscopy: Saline wet mount: vaginal discharge is sampled with a cotton tipped swab. The sample of the vaginal discharge is then mixed with several drops of 0.9 % normal saline solution at room temperature, and a sample of this solution is placed on a glass slide followed by a cover slip. The slide is then examined under a microscope at low and high power. Microscopy should be performed ideally within 10–20 min of obtaining the sample to reduce the possibility of loss of motility of any trichomonads.

  Microscopic evaluation of normal vaginal discharge should reveal a predominance of squamous epithelial cells, rare polymorphonuclear leukocytes (PMNs), and lactobacilli. The primary goal of the examination is to look for candidal buds or hyphae, motile trichomonads, epithelial cells studded with adherent

coccobacilli termed "clue cells", and increased number of PMNs. Excess PMNs without evidence of yeast, trichomonads, or clue cells suggest cervicitis.

Potassium hydroxide wet mount: the addition of 10 % potassium hydroxide (KOH) to the wet mount of vaginal discharge destroys cellular elements; thus, it is helpful for identifying budding yeast for the diagnosis of candidal vaginitis.

Amine test: smelling the slide immediately after KOH is applied, also called the "whiff test" is helpful if an amine "fishy" odor is identified, this indicates bacterial vaginosis.

- Other tests: DNA tests or cultures for *Neisseria gonorrheae* or *C. trachomatis* should be obtained in patients with a purulent discharge, cervical friability, any symptoms suggestive of PID, or leukocytes on microscopy. Such tests should also be performed in women who fall into higher-risk groups where annual screening is recommended (Workowski and Bolan 2015).

Because the normal vaginal flora is very heterogeneous, routine bacterial cultures of the vagina have no use in diagnosing bacterial vaginosis. They may have a limited role in diagnosing suspected cases of group A streptococcal vaginitis, but this condition is considered rare. In patients with symptoms suggestive of bacterial vaginosis that do not fulfill Amsel's criteria [presence of abnormal gray discharge vaginal pH greater than 4.5, a positive amine test, and more than 20% of the epithelial cells are clue cells], a Gram stain is considered the criterion standard for diagnosis (American College of Obstetricians and Gynecologists 2015).

In selected patients, vaginal cultures or polymerase chain reaction tests for *Trichomonas* or yeast are helpful. If microscopy is not available, or depending on provider preference and comfort with microcopy, other currently available ancillary tests for diagnosing vaginal infections include rapid tests for enzyme activity from bacterial vaginosis-associated organisms, *Trichomonas vaginalis* antigen, and point-of-care testing for DNA of *G. vaginalis*, *T. vaginalis*, and Candida species; however, the role of these tests in the proper management of patients with vaginitis is unclear. When available a vaginal Gram stain for Nugent scoring of the bacterial flora may help to identify patients with bacterial vaginosis (Sobel 2016a). Nugent scoring is a based on the presence of Gram positive rods [*Lactobacillus*], small Gram-variable rods [*Gardnerella*] and curved Gram-variable rods [*Mobiluncus*].

Other organisms routinely found on vaginal culture include group B streptococci (GBS) and lactobacilli. GBS is part of the normal flora in approximately 25 % of women and, as a result, is frequently isolated in women with vaginal symptoms. However, there is no association between women with GBS and vulvovaginal symptoms (Shaw et al. 2003). Similarly, lactobacilli are also part of the normal vaginal flora. Although it has been hypothesized that an overgrowth of lactobacilli can cause vaginal symptoms (Cibley and Cibley 1991), such a syndrome is poorly characterized, and controlled studies confirming the existence of such a syndrome are lacking. Thus, the presence of large numbers of lactobacilli on either microscopy or vaginal culture should be considered a normal finding (American College of Obstetricians and Gynecologists 2015).

8 Treatment

- Vaginal candidiasis: The diagnosis should be further classified as uncomplicated or complicated vulvovaginal candidiasis. This classification system has treatment implications because complicated vulvovaginal candidiasis is more likely to fail standard antifungal therapy (Sobel et al. 1995).

Uncomplicated vulvovaginal candidiasis is defined as:

- Sporadic, infrequent episodes ($\leq$3 episodes/year)
- Mild to moderate signs/symptoms

– Probable infection with *Candida albicans*
– Healthy, nonpregnant woman

Women with uncomplicated vulvovaginal candidiasis can be treated successfully with any of the options listed in Table 1. Topical treatments can cause local side effects, such as burning and irritation in some patients, exacerbating symptoms. Occasionally, oral therapy may cause systemic side effects, such as gastrointestinal intolerance, headache, and liver function test elevations; these usually are mild and self-limited (Sobel et al. 1995). Allergic reactions to oral therapy are rare. Because all listed antifungal treatments seem to have comparable safety and efficacy, the choice of therapy should be individualized to the specific patient and her preferences. Clinicians should take factors such as cost, convenience, compliance, ease of use, history of response or adverse reactions to prior treatments, and patient preference into consideration when choosing treatment options.

Complicated vulvovaginal candidiasis is defined as including one or more of the following criteria:

– Severe signs/symptoms
– Candida species other than *C. albicans*, particularly *C. glabrata*
– Pregnancy, poorly controlled diabetes, immunosuppression, and debilitation
– History of recurrent (≥4/year) culture-verified vulvovaginal candidiasis

Patients with complicated vulvovaginal candidiasis typically require more aggressive treatment to achieve relief and resolution of symptoms:

- In a placebo-controlled randomized trial of women with severe vulvovaginal candidiasis, a second dose of fluconazole, 150 mg given 3 days after the first dose, increased the cure rate from 67 % to 80 % (Sobel et al. 2001).
- In women with recurrent vulvovaginal candidiasis secondary to *C. albicans*, after initial intensive therapy for 7–14 days to achieve mycologic remission, prolonged antifungal treatment with fluconazole, 150 mg weekly (Sobel et al. 2004) for 6 months, will successfully control more than 90 % of symptomatic episodes and will lead to a prolonged protective effect in approximately 50 % of women.
- Although daily oral ketoconazole was previously described as an effective suppressive therapy in women with recurrent vulvovaginal candidiasis (Sobel 1986), weekly fluconazole has a lower risk of liver toxicity and should be used instead of ketoconazole (Workowski and Bolan 2015)
- For patients who are unable or unwilling to take fluconazole, prolonged maintenance therapy with intermittent topical agents, such as clotrimazole, 500 mg weekly or 200 mg twice a week, are acceptable options (Workowski and Bolan 2015).

For a small subset of patients with chronic vulvovaginal candidiasis, there is some evidence that a more frequent daily dosing regimen of fluconazole 50–100 mg daily is able to achieve long-term symptoms remission with minimal adverse outcomes or side effects (Nguyen et al. 2016).

Pregnant women may have more frequent colonization with Candida species and more frequent symptomatic vulvovaginal candidiasis than nonpregnant women. Although low-dose short-term fluconazole use is not associated with known birth defects, higher doses of 400–800 mg/day have been linked to birth defects. Thus, treatment of vulvovaginal candidiasis in pregnancy should consist of one of the topical imidazole therapies listed in Table 1, probably for 7 days (Xu et al. 2004; American College of Obstetricians and Gynecologists 2015).

Although much less common than *C. albicans*, vulvovaginal candidiasis caused by non-albicans Candida species are less likely to respond to azole antifungal therapy (Sobel et al. 2001). Current experience consists exclusively of descriptions of case series of patients seen at centers specializing in the treatment of vaginitis. A standard course

Table 1 Therapy for vulvovaginal infections

Indication	Drug	Formulation	Dosage	Duration
Uncomplicated Candidiasis	Butoconazole	2 % sustained-release formula	5 g daily	1 day
	Clotrimazole	1 % cream	5 g daily	7 days
		2 % cream	5 g daily	3 days
		100 mg vaginal suppository	100 mg daily	7 days
		200 mg vaginal suppository	200 mg daily	3 days
		500 mg vaginal suppository	500 mg daily	1 day
	Fluconazole	150 mg oral tablet	10 mg daily	1 day
	Miconazole	2 % cream	5 g daily	7 days
		100 mg vaginal suppository	100 mg daily	7 days
		200 mg suppository	200 mg daily	3 days
		1200 mg vaginal suppository	1200 mg daily	1 day
	Nystatin	100,000 units vaginal tablets	Daily	14 days
	Terconazole	0.4 % cream	5 g daily	7 days
		0.8 % cream	5 g daily	3 days
	Tioconazole	2 % cream	5 g daily	3 days
		6.5 % cream	5 g daily	1 day
Bacterial vaginosis	Clindamycin	2 % cream	5 g daily	7 days
		2 % sustained release cram	5 g daily	1 day
		100 mg ovules	100 mg daily	3 days
		300 mg oral	300 mg twice daily	7 days
	Metronidazole	0.75 % gel	5 gg daily	5 days
		500 mg oral	500 mg twice daily	7 days
Trichomoniasis	Metronidazole	500 mg oral	4 tabs as one dose	1 day
			500 mg twice daily	7 days
	Tinidazole	500 mg oral	4 tabs as one dose	1 day

Adapted from American college of Obstetricians and Gynecologists (2015)

of topical imidazole therapy may be effective in up to 50 % of such cases (Sood et al. 2000).

- Therapy with vaginal boric acid, 600-mg capsules daily for a minimum of 14 days, may be effective for azole failures (Sobel et al. 2003). Patients with non-albicans Candida vulvovaginal candidiasis in whom boric acid therapy is ineffective should be referred to a specialist experienced in handling such cases.

8.1 Bacterial Vaginosis

A clinical diagnosis of bacterial vaginosis requires the presence of three out of four Amsel's criteria: abnormal gray discharge, vaginal pH greater than 4.5, a positive amine test, and more than 20 % of the epithelial cells are clue cells. In research settings, the Nugent score, which assigns a value to different bacterial morphotypes seen on Gram stain of vaginal secretions, is considered the current criterion standard for diagnosing bacterial vaginosis. Compared to Nugent scoring, Amsel's criteria have a sensitivity of 92 % and specificity of 77 %. However, a similar sensitivity and specificity have been demonstrated by using any combination of only two clinical criteria (Gutman et al. 2005).

Nonpregnant women with bacterial vaginosis can be treated with the alternatives listed in Table 1. The listed alternatives are considered to have comparable clinical efficacy and safety; however, clindamycin use may be associated with in vitro antimicrobial resistance (American College of Obstetricians and Gynecologists 2015). Generally, topical therapy is more expensive than generic oral metronidazole, although

oral treatment may be associated with significant gastrointestinal symptoms. Disulfiram [Antabuse] like reactions may occur with both oral and topical metronidazole if alcohol is also consumed temporarily. As with the treatment of vulvovaginal candidiasis, treatment for BV should be individualized to the patient after considering multiple clinical factors.

In several epidemiological studies, bacterial vaginosis has been associated with low birth weight, premature rupture of membranes (PROM), and prematurity (American College of Obstetricians and Gynecologists 2015) (Gravett et al. 1986).

Standard antibiotic therapy seems to effectively eradicate bacterial vaginosis in pregnant women, and those with symptomatic bacterial vaginosis should be treated. Neither metronidazole nor clindamycin have known teratogenic effects (American College of Obstetricians and Gynecologists 2015). Studies conducted to determine whether treating asymptomatic bacterial vaginosis in an uncomplicated pregnancy will decrease the risk of adverse outcomes have yielded conflicting results. Presently there is no clear benefit to routine screening and treatment in US populations (American College of Obstetricians and Gynecologists 2015). Although in women with high-risk pregnancies, particularly those with prior preterm deliveries, some studies have shown that screening for and treating bacterial vaginosis with oral metronidazole may decrease the risk of preterm PROM and preterm delivery (Morales et al. 1994), others have not shown benefit. (Carey et al. 2000).

Treatment for BV before abortion or hysterectomy significantly decreases the risk of postoperative infectious complications (Koumans and Kendrick 2001). Treatment also helps women to resolve concurrent mucopurulent cervicitis. There are no current data on the treatment of BV to decrease acquisition of PID, HIV, or HSV-2, and the role of treatment of asymptomatic bacterial vaginosis to prevent these associated morbidities is unclear (American College of Obstetricians and Gynecologists 2015).

Following treatment, bacterial vaginosis may recur in up to 30 % of women within 3 months (Wilson 2004). Possible mechanisms include persistence of pathogenic bacteria; reinfection from exogenous sources, including a sexual partner; or failure of the normal *Lactobacillus*-dominant flora to reestablish themselves. Studies of partner treatment have failed to show a protective effect.

Studies of recolonization with *Lactobacillus* supplements have used nonvaginal strains of *Lactobacillus* and have failed to show a clear benefit (Wilson 2004).

Prolonged antibiotic therapy may be useful in women with recurrent bacterial vaginosis; however, further investigation is warranted (American College of Obstetricians and Gynecologists 2015).

8.2 Trichomoniasis

A clinical diagnosis of trichomoniasis requires the presence of trichomonads on microscopy or a positive culture, NAAT, or rapid antigen test. The presence of trichomonads on cervical cytology is not sensitive and can be a false positive; thus, asymptomatic women with trichomonads identified on a conventional Pap smear or liquid based test should be evaluated by wet mount. If the wet mount is negative, a NAAT, culture, or rapid test is indicated, and treatment is warranty after the diagnosis is confirmed (Sobel 2016e).

Treatments for uncomplicated trichomoniasis are listed in Table 1. Although metronidazole has been the mainstay of treatment in the United States, tinidazole is also approved as single-dose therapy. Both treatments seem to be equally efficacious (Workowski and Bolan 2015) and have side effects of a similar nature including gastrointestinal upset and a possible Disulfiram-like effect.

1. Because of this all patients should be advised to avoid alcohol for 24 h after metronidazole

use and 72 h after tinidazole use (Workowski and Bolan 2015).
2. Partners of women with trichomoniasis should also be treated.
3. In cases of metronidazole allergy, patients may be referred for desensitization to and treatment with metronidazole. There are no data on cross-reactivity between tinidazole and metronidazole.

Metronidazole is considered safe to use in pregnancy; however, data on tinidazole are too limited to be of use. Thus, Metronidazole is the treatment of choice in pregnancy.

Like bacterial vaginosis, trichomoniasis has been associated with adverse outcomes such as preterm delivery, PROM, and low birth weight.

Although a study of treatment for asymptomatic trichomoniasis in pregnant women showed an increased preterm delivery rate in the treated group, it should be noted that 23 % of the women in the placebo group received metronidazole outside the protocol and treatment occurred at advanced gestational age. Therefore, these results may not apply to a broader population of pregnant women (Klebanoff et al. 2001). However, the results of this study suggest that treatment of trichomoniasis during pregnancy does not help to prevent associated adverse sequelae.

Oral treatment is preferred to vaginal therapy since systemic administration achieves higher drug levels and therapeutic drug levels in the urethra and periurethral glands, which can serve as endogenous reservoirs of organisms that can cause recurrence.

Cure rates for vaginal therapy with metronidazole gel are $\leq$50 %, and therefore vaginal therapy with metronidazole is not recommended (Yudin et al. 2003).

Although high-level resistance to metronidazole is considered rare, low level in vitro resistance may be as high as 5 % (Schmid 2001). In suspected cases of resistance, patients should be interviewed carefully to exclude the possibility of noncompliance with the medication regimen or reinfection from an untreated partner. Sending the resistant isolate to a reference laboratory that can perform susceptibility testing should be considered to help guide choice and dosing of therapy (Workowski and Bolan 2015) in complicated resistant cases.

It is recommended to retest all women treated for a documented *Trichomonas* infection, regardless of whether they believe their sex partners were treated.

Centers for Disease Control and Prevention (CDC) recommend repeat testing with a nucleic acid amplification test (NAAT) as soon as 2 weeks after and within 3 months of completing treatment (Workowski and Bolan 2015). The rationale for repeat testing is that reinfection rates of up to 17 % have been reported in women treated for trichomoniasis.

Treatment of sex partners is indicated because maximal cure rates in infected women are achieved when their sexual partners are treated simultaneously (Workowski and Bolan 2015).

Concurrent treatment also prevents transmission to other sexual contacts. It is not mandatory to identify the organism in a male partner before treating him (i.e., expedited partner therapy [EPT]), given the high rate of concurrent carriage (30–70 %), difficulty of diagnosis in males, lower compliance when the partner is asked to visit his health-care provider, and the convenience, low morbidity, and low cost of empiric treatment (Sobel 2016e). Treatment of sex partners is the same as nonpregnant females, with preference for a single-dose regimen to maximize compliance (i.e., single oral dose of either tinidazole or metronidazole 2 g).

Patients should abstain from intercourse until both partners have completed treatment; otherwise, reinfection can occur.

8.3 Other Causes of Vulvovaginal Symptoms

Patients with atrophic vaginitis may have an abnormal vaginal discharge, dryness, itching, burning, or dyspareunia. Physical findings include thinning of the vaginal epithelium, loss of elasticity, loss of rugae, pH $\geq$5, vaginal erosions, and cervicovaginal friability. The wet mount is nonspecific, as similar findings occur in other inflammatory vaginal conditions. It shows parabasal cells, many polymorphonuclear leukocytes (PMNs), no lactobacilli, and with or without background bacteria. Parabasal cells are immature squamous epithelial cells that are rounded and have a large nucleus-to-cytoplasm ratio; in contrast, mature squamous epithelial cells are larger, cuboidal, with a smaller nucleus-to-cytoplasm ratio, and sometimes folded (Bachman and Santen 2016a).

Although atrophic vaginitis is more common in postmenopausal women, sometimes it can be observed in younger premenopausal women. Treatment generally consists of local water-based moisturizing preparations or topical or systemic estrogen. Symptoms of vaginal dryness can be managed by regular use of vaginal moisturizing agents one or more times per week with supplemental use of vaginal lubricants for sexual intercourse. There are many products available ranging from simple organic coconut oil to a myriad of commercial brands (examples include Replens, Pre-Seed, Me Again, Vagisil Feminine Moisturizer, Feminease, and K-Y SILK-E). While these agents may improve coital comfort and increase vaginal moisture, they do not reverse most atrophic vaginal changes. They are most useful for women with mild symptoms and those for whom they provide sufficient comfort during coital activity (Bachman and Santen 2016b).

Estrogen is the most effective treatment for moderate to severe symptoms of vaginal atrophy. The use of estrogen therapy is appropriate for women with symptoms of vaginal atrophy in the setting of a relative hypoestrogenic state, if there are no contraindications to this therapy (e.g., certain women with estrogen-dependent tumors).

Adequate estrogen therapy leads to restoration of the normal vaginal acidic pH and microflora, thickening of the epithelium, increased vaginal secretions, and decreased vaginal dryness. These patients should have a symptomatic response to topical estrogen therapy, and antibiotics are not needed. If symptoms do not respond to topical estrogen, then other diagnoses should be considered.

Desquamative inflammatory vaginitis (DIV) (Sobel 1994) is a rarer but well-defined form of vaginitis. Generally, DIV occurs in perimenopausal or postmenopausal women and causes burning, dyspareunia, and an abnormal yellow or green discharge. Although streptococcal species, including GBS, are found in more than 90 % of affected women, this does not mean that desquamative inflammatory vaginitis is caused by streptococcal species. Examination reveals a purulent discharge with varying amounts of vestibular and vaginal erythema. The vaginal pH is elevated and the amine test result is negative. Microscopy reveals large amounts of polymorphonuclear cells and parabasal cells. No randomized trials of treatment approaches have been reported. The two most common treatments are intravaginal clindamycin and/or glucocorticoids (Sobel 1994)

Options for initial therapy for DIV include one of the following:

Two percent clindamycin cream 4–5 g intravaginally once daily

Ten percent hydrocortisone cream 3–5 g intravaginally once daily (compounded)

Hydrocortisone 100 mg/g in clindamycin 2 % emollient cream base (compounded) 5 g (one applicator full) intravaginally every other day.

Treatment is typically prescribed for 4–6 weeks and leads to dramatic improvement in symptoms in most patients. The patient is seen in

follow-up after 4 weeks. If complete clinical and microscopic remission is achieved, defined as complete absence of signs and symptoms of disease and no increase in leukocytes or parabasal cells on saline microscopy, treatment can be stopped. If she has improved but is not in complete remission, treatment is continued until complete remission is achieved; this may take another two or more weeks. Vaginal pH will return to normal when remission is achieved, except in women on clindamycin since clindamycin reduces colonization by lactobacilli. Upon complete remission, therapy is discontinued, and the patient is followed monthly for several months to ensure that remission is maintained.

If there has been no or poor improvement after the initial 4 weeks of therapy, other diagnoses in the differential diagnosis should be considered; if these diagnoses are excluded, the clinician can switch to a different therapy or add an additional agent, e.g., from clindamycin to hydrocortisone or both agents together compounded, for a 4–6-week course. Relapse after therapy is fairly common (Sobel 2016d).

9 Women Without a Diagnosis After the Initial Evaluation

After initial diagnostic evaluation 25–40 % of patients with genital symptoms do not have a specific cause identified (Baron et al. 2013). Initially the three most common infectious causes of vaginitis, Candida vaginitis, bacterial vaginosis, and trichomoniasis must be excluded. Once these have been ruled out, then the following principles apply:

- If the patient has minimal symptoms at the time of evaluation and the evaluation was nondiagnostic, then the evaluation should be repeated at a second visit when she is symptomatic.
- Avoid empiric blind therapy, which can often aggravate symptoms.
- Determine vaginal pH as it will often guide the differential diagnosis:
  - If pH is increased, consider noninfectious causes of vaginal symptoms such as vaginal atrophy (in lactating women or postmenopausal women), erosive lichen planus, lichen sclerosis, desquamative inflammatory vaginitis, and pemphigoid syndromes.
  - If pH is normal, the vagina is likely to be normal with normal microbiome, so focus on the most common vulvar and external causes of vulvovaginal symptoms, such as contact irritant dermatitis, seborrhea or eczematous dermatitis, and psoriasis.
- Obtain information on the duration of symptoms (acute versus chronic symptoms), site of symptoms (vulva versus vagina), and whether there has been recent change in sexual partner/practices, or change in hygienic habits, as this information is also helpful in forming a differential diagnosis.

Obtaining a detailed history including the following information may be helpful in diagnosis:

- Estrogen status: In menopausal, perimenopausal, or otherwise hypoestrogenic women, atrophic vaginitis is a common cause of vaginitis symptoms. In premenopausal women, hypoestrogenic settings include the postpartum period, lactation, and during administration of antiestrogenic drugs (and sometimes with low estrogen levels related to low-dose oral contraceptives). Menopausal women receiving hormone therapy may not have adequate estrogen levels for vaginal epithelial maintenance and thus remain prone to atrophic vaginitis symptoms.
- Acuity and timing of symptoms: An acute process is more likely to have an infectious etiology; a chronic process is more likely from inflammation unrelated to infection. If the woman has had recurrent episodes of vaginitis, verify the results of prior diagnostic testing, the type of therapy used, her response to this therapy, and number of episodes in the last year.
- Associated symptoms: Inquire about pelvic pain or systemic symptoms (e.g., fever, nausea). Pelvic pain is suggestive of pelvic

inflammatory disease (PID) and suprapubic pain is suggestive of cystitis; however, both are rare with vaginitis alone. The common causes of vaginitis are not associated with systemic symptoms.

– Sexual practices: The patient's current sexual practices and the gender of her sex partner may be informative. Women who have sex with women are at increased risk of bacterial vaginosis. Examples of changes that may impact vaginal symptoms are exposure to a new sexual partner, a new lubricant or substance being used in the vagina, and anal sex followed by vaginal penetration. A new sexual partner increases the risk of acquiring sexually transmitted infections such as *Trichomonas vaginalis* or cervicitis related to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.
– Medications: Medications (prescription and nonprescription) may impact vaginal symptoms. Antibiotics predispose to candidal vulvovaginitis; estrogen-progestin contraceptives can increase physiologic discharge; pruritus and burning unresponsive to antifungal agents may be due to vulvovaginal dermatitis.
– Hygienic practices: Hygienic practices may reveal causes of symptoms. Mechanical, chemical, or allergic irritation may cause vulvovaginal symptoms (pruritus, burning) mistakenly attributed to an infectious source. Vaginal symptoms can result from irritants (e.g., scented panty liners, spermicides, povidone-iodine, soaps and perfumes, depilatories, wax, and some topical drugs) and allergens (e.g., latex condoms, topical antifungal agents, seminal fluid, chemical preservatives) that produce acute and chronic hypersensitivity reactions, including contact dermatitis. **Keeping the vulva clean and dry is an important goal for curing and healing.**
– Medical history: History of an oral mucosal, ocular, cutaneous, or systemic disease that could affect the vulvovaginal area is an important information. For example, herpes simplex virus and Behçet's syndrome can cause vulvovaginal ulcers. Women with diabetes are prone to vulvovaginal candidiasis. Women with human immunodeficiency virus (HIV) are prone to vaginal infections. After transplantation, graft versus host disease can cause vaginal irritation, discharge, ulceration, and stenosis (Zantomio et al. 2006; Spiryda et al. 2003). Stevens-Johnson syndrome and toxic epidermal necrolysis have potentially severe vulvovaginal sequelae.
– Surgical History: Recent transvaginal surgery, cervical procedures such as a LEEP or cryotherapy of the cervix or repair of perineal lacerations from childbirth may cause changes in vaginal discharge and symptoms. Vaginal symptoms may be related to a foreign body, bacterial infection, or granulation tissue.
– Irritants and allergens: Vaginal discharge can result from irritants (e.g., pads, scented panty liners, spermicides, povidone-iodine, soaps and perfumes, and some prescription and nonprescription topical medications) and allergens (e.g., latex condoms, topical antifungal agents, seminal fluid, chemical preservatives) related to commonly used products that can produce acute and chronic hypersensitivity reactions, including contact dermatitis. Diagnosis and management involve systematically removing potential irritants and allergens from the urogenital environment (Table 2). Corticosteroid therapy is indicated to control inflammation and relieve symptoms locally as needed. It is recommended to use a medium potency fluorinated topical steroid two to three times per day, as needed, until symptoms resolve.

Some women may have pruritis with a negative Candida culture. Patients may complain of pruritus that can occur anywhere in the lower genital tract: the vagina, vestibule, vulva, perineum, or perianal area. It may be unilateral or bilateral and often women are unable to clearly localize the site or source. Infrequent, transient, mild vulvovaginal pruritus is relatively common and may be normal; patient reassurance is necessary. Further workup and evaluation are indicated in women with persistent, chronic, or severe pruritus. Discussing vaginal hygiene including an emphasis on cleaning and drying the vulva may be helpful.

Table 2 Causes of vulvar contact dermatitis

Irritants	Allergens
Soap, bubble bath, shampoo	Benzocaine
Sanitary or incontinence pads, tampons	Neomycin
Nylon underwear	Chlorhexidine (e.g., in lubricants, antiseptic washes)
Sweat, urine	Ethylene diamine (e.g., hydroxyzine)
Talcum powder	Fragrances
Vaginal or vulvar medications	Balsam of Peru (Myroxylon pereirae), fragrance (e.g., in soaps, feminine products)
Douches	Propylene glycol, formaldehyde-releasing preservatives, and other preservatives (e.g., methylchloroisothiazolinone and methylisothiazolinone in moist flushable wipes)
Vaginal hygiene products	Tea tree oil
Methylated spirits	Natural rubber (latex) and synthetic rubber (nitrile) (e.g., condoms, diaphragms)
Tea tree oil	Semen
Pinetarsol	Disinfectants
Alcohol	Lanolin
Fragrances	Dyes
Deodorants	Nickel
Hair conditioner	
Chemically-treated clothing, toilet paper, or water	

Adapted from Johnson et al. (2016)

Candida is the most common infectious cause of vulvovaginal pruritus, followed by trichomoniasis. When initial workup of infectious causes is negative, noninfectious causes must be considered such as contact dermatitis, either allergic or chemical-induced dermatitis, is the most common noninfectious etiology. Allergens/irritants include soaps, creams, microbicides, toilet paper, detergents, and sanitary pads (see Table 2).

Vulvar dermatoses also account for a substantial proportion of noninfectious cases and include lichen sclerosus, lichen planus, and lichen simplex chronicus. Other common skin conditions that may present with external pruritus include psoriasis, eczema, and seborrheic dermatitis. Vulvar pruritus is the most common complaint among symptomatic women with vulvar intraepithelial neoplasia; other presentations include a visible lesion, a palpable abnormality, perineal pain or burning, or dysuria.

Treatment begins with removing potential causes of pruritus from daily life (see Table 3 for hygienic practices). Empiric drug therapy should be avoided. Targeted drug therapy is administered when a specific cause is identified. Biopsy should be considered depending on presence of a lesion or persistent symptoms.

– Serosanguinous discharge and pelvic pain: The overall incidence of fallopian tube carcinoma is low; however, it typically presents in women in the fifth or sixth decades of life with vague complaints. The type and frequency of described symptoms and findings associated with this malignancy are serosanguineous vaginal discharge (50–60%), pelvic pain (30–50%), and pelvic mass (12–61 %); however, the full triad (Latzko's triad) is noted in fewer than 15 % of patients (Sobel 2016a).
– Chronic introital pain: Vestibulodynia refers to spontaneous or induced pain on penetration of the introitus and tenderness provoked by focal vestibular pressure as the primary symptom. These symptoms should be present for at least 3–6 months, and other causes of vestibular pain, such as infectious or atrophic vaginitis, should be excluded before making the diagnosis. Vaginal discharge and vaginal inflammation are typical features of vaginitis but are not

Table 3 Healthy vulval hygiene practices

Avoid	Substitute
Pantyhose	Stockings with a garter belt, thigh high or knee high stockings
Synthetic underwear	Cotton underwear or no underwear
Jeans and other tight pants	Loose pants, skirts, dresses
Swimsuits, leotards, thongs, lycra garments	Loose fitting cotton garments
Panty liners	Tampons or cotton pads
Scented soaps or shampoos	Fragrance free pH neutral soap
Bubble baths	Tub baths in the morning and at night without additives and at a comfortable temperature
Scented detergents	Unscented detergents
Washcloths	Use fingertips for washing, pat dry, don't rub dry
Baby wipes or flushable wipes	Rinse with water using a sports water bottle or perineal irrigation bottle
Feminine sprays, douches, powders	These are not necessary products and can be omitted from personal hygiene practices.
Dyed toilet articles	Toilet articles without dyes
Hair dryers to dry vulva skin without contact	Dry vulva by gentle patting

Adapted from Johnson et al. (2016)

part of the clinical spectrum of vestibulodynia. Candidal vulvovaginitis may mimic localized, provoked vulvodynia, and may also be an initial trigger for this condition.

– Postcoital vulvovaginal pruritus and pain: Seminal plasma allergy or hypersensitivity is characterized by postcoital vulvovaginal pruritus, burning, edema, and erythema with or without other systemic symptoms. Complaints occur immediately to within 1 h after contact with seminal plasma and vaginal discharge is not a typical feature. Overall it is a rare disorder, and most affected women are under age 40 years and have a family history of atopy. The diagnosis can be made based on absence of symptoms with condom use and on positive skin testing with a sample of seminal fluid.
– Persistent genital malodor: Persistent genital malodor can seriously impact a woman's quality of life. A normal vaginal odor is difficult to define; however, it could be described as slightly sour due to lactic acid and volatile sulfur compounds typically present in normal vaginal discharge. For patients complaining of a persistent malodor, the cause may be difficult to identify after readily diagnosable causes have been excluded. These causes include:

Neglected foreign body (including retained tampon)
Bacterial vaginosis
Trichomoniasis
Infectious ulcer/pelvic inflammatory disease (PID)
Pelvic fistula (rectovaginal, vesicovaginal, ureterovaginal)
Hidradenitis suppurativa
Chronic constipation
Metabolic disorder
Urinary incontinence
Fecal incontinence
Poor hygiene
Malignant ulcer
Excessive genital perspiration and local bacterial colonization related to obesity

When the malodor is perceived only by the patient, olfactory reference syndrome and olfactory hallucinations may be considered.

Management depends on determining a cause. In the absence of poor hygiene, frequent washing and vaginal douching are not helpful and can be harmful to the patient's vaginal health. Excessive soaping of the genital area can cause a chemical dermatitis creating additional symptoms, and

douching can increase the risk of vaginal and pelvic infection (American College of Obstetricians and Gynecologists 2015). Frequently a cause is not established.

10 Post Diagnostic Management

Women with a confirmed diagnosis are treated with the appropriate treatment as determined by the diagnostic workup and provided reassurance. Follow-up is guided by the diagnosis and patient response to treatment.

Patients with sexually transmitted infections may have an infected partner and are at increased risk of acquiring other sexually transmitted diseases. Thus, sexual partners should be referred for specific testing and treatment; partner delivered patient medication (PDPM) is an alternative. Patients who continue to exhibit symptoms and/or have positive tests for sexually transmitted infections after treatment are likely to have been reinfected by their sexual partner.

11 Conclusion

Women increasingly rely on self-diagnosis and self-treatment of vulvovaginal symptoms. However, the reliability of self-diagnosis may be poorer than previously suggested. Vulvovaginal symptoms are often nonspecific; thus, patients who are already in the office should not be treated for vaginitis without an examination. Clinical evaluation of women with vaginal symptoms should be encouraged, particularly for women who fail to respond to self-treatment with a nonprescription antifungal. Microscopy is the first line for diagnosing vulvovaginal candidiasis and trichomoniasis. In selected patients, culture for yeast and *T. vaginalis* should be obtained in addition to standard office-based testing. Women with complicated vulvovaginal candidiasis should receive more aggressive treatment than women with an uncomplicated episode. Douching is not recommended for the prevention or treatment of vaginitis. Vaginal hygiene including gentle cleaning and drying the vulva may be an appropriate discussion.

After exclusion of pathological causes of vaginal discharge, women with a change in their normal vaginal discharge can be reassured that changes in the volume and character of vaginal discharge are normal and can be due to changes in diet, sexual activity, medication, stress, etc.

Currently no dietary modifications are relevant in management of vaginitis, except for avoiding excessive refined sugars in some women prone to Candida vulvovaginitis. Similarly, probiotics available to women in the United States are not proven to be useful in prevention or control of vaginitis.

12 Cross-References

- ▶ Benign Disease of the Vulva
- ▶ Benign Vulvar and Vaginal Pathology
- ▶ Malignant Vulvar and Vaginal Pathology
- ▶ Management of Menopausal Symptoms
- ▶ Management of Sexual Dysfunctions
- ▶ Management of Vaginal and Vulvar Lesions in the Older Woman
- ▶ Management of Vulvodynia
- ▶ Menopausal Hormone Therapy
- ▶ Preinvasive Epithelial Disease of the Vulva

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Management of Chronic Recurrent Vulvovaginitis

Abigail Kingston and Emma Torbé

Contents

Abstract

Vulvovaginitis is the most common reason why women present to a gynecologist. The term covers inflammation or infection of the vagina and/or vulva. Women with symptoms lasting for more than 6 months experience chronic vulvovaginitis. The clinical presentation of women with vulvovaginitis is similar regardless of the underlying cause and so a careful history is important. Symptoms include itching, discharge, irritation, dysuria, vaginal odor, rash, and burning. Other findings on exam include erythema, edema and excoriation of the vulvar skin, ulceration, or chronic vulvar skin changes. The following investigations can aid diagnosis: vaginal pH, amine whiff test, vulvar biopsy, fungal cultures, and wet smears. Causes fall into four main groups, infections, dermatoses, atrophy, and neoplasia. Infectious causes include bacterial vaginosis, vulvovaginal candidiasis, *Trichomonas vaginalis*, and threadworms (pinworms). Symptoms will improve following effective treatment of the infection. Vaginal atrophy is a result of estrogen deficiency and is improved with estrogen replacement. Dermatoses include lichen sclerosus, lichen planus, contact dermatitis, and lichen simplex. Treatment of dermatoses includes steroids, topical estrogens, tacrolimus ointment, retinoids, and emollients. All women will benefit from good vulvar skin care and emotional support.

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Vulvovaginitis • Bacterial vaginosis • Vulvovaginal candidiasis • *Trichomonas vaginalis* • Atrophic vaginitis • Contact dermatitis • Lichen simplex • Lichen sclerosus • Lichen planus • Threadworms

1 Introduction

The term vulvovaginitis is very general and is used by medical professionals to cover inflammation or infection of the vagina and/or the vulva. It is one of the top 25 reasons why women seek medical care and is the most common reason that women present to a gynecologist (Kent 1991). As so many women suffer with this condition, it is not surprising that there is a subgroup with chronic vulvovaginitis (symptoms lasting for more than 6 months). Etiologies fall into four main groups: infections, dermatoses, atrophy, and neoplasia:

- Infections – *Trichomonas vaginalis*, bacterial vaginosis, vulvovaginal candidiasis, and threadworms.
- Atrophy – atrophic vaginitis.
- Dermatoses – lichen sclerosus, lichen planus, contact dermatitis, and lichen simplex.
- Neoplasia – many women with squamous cell carcinoma experience vulva irritation.

2 Pathophysiology

During a woman's reproductive years, the vagina maintains a moist environment that fluctuates during the menstrual cycle. Estrogen causes the vaginal nonkeratinized stratified squamous epithelium to be thick, rugated, and elastic by maintaining the epithelial collagen content. Estrogen also causes the epithelium to be rich in glycogen. The vaginal epithelium and cervical glands secrete an alkaline transudate resulting in a moist environment. The microflora of the vagina forms an environment that is unique and balanced. While it reacts to external stimuli, once the stimuli are removed, the vaginal environment returns to normal. The bacterial flora of a healthy vagina is made up of many microorganisms both aerobic and anaerobic gram-positive bacteria and gram-negative bacteria. *Lactobacillus* and *Corynebacterium* predominate over other bacteria *Streptococcus*, *Bacteroides*, *Staphylococcus*, and *Peptostreptococcus*. *Lactobacillus* and *Corynebacterium* produce lactic and acetic acid from glycogen that lowers the vaginal pH resulting in a normal pH ranging from 3.8 to 4.5. The optimal/normal vaginal discharge is clear, thin, and odorless and is between 1 and 4 ml/day although the presence of thick, white discharge with mild odor occurs in asymptomatic women and is not considered abnormal.

Vaginal pH increases with age, menses, cervical mucus associated with ovulation, contraceptive choice, sexual activity, ejaculation, pregnancy, rupture of membranes in pregnancy, exposure to exogenous hormones, antibiotics, use of hygiene products, douching, foreign bodies in the vagina, high sugar diet, and infections (trichomoniasis, bacterial vaginosis, group A streptococcal infection).

The vulvar skin is sensitive to the vaginal environment as well as hormonal, metabolic, and allergic influences. The most significant change occurs during the menopause where there is a compromise in the vulva's barrier function. This is due to both estrogen deficiency and aging, resulting in a rise in pH and a decrease in the antimicrobial defenses of the skin. There is concomitant loss of lipid production that slows healing in response to injury, and there is an increased risk of infections due to an age-related decline in cell-mediated immunity (Summers and Hunn 2007).

3 Presenting Symptoms

The symptoms of vulvovaginitis are varied and common, and many medical therapies for treatment or symptomatic relief are available to purchase over-the-counter. Although there is an expectation and an acceptance that women are capable of self-medication, the accuracy of women to correctly self-diagnose is poor leading

many to inappropriate medications, sometimes exposing themselves to irritant dermatitis and perpetuating symptoms (Nyirjesy et al. 1997). It is therefore essential that a clinician takes a full history and performs a careful examination, particularly in those with chronic symptoms, to establish a correct diagnosis and direct correct treatment. In the United States, an estimated $250 million is spent annually, on over-the-counter antifungal therapies, the most common medication used for vulvar itching or discharge.

Clinical presentations of women with vulvovaginitis are often similar regardless of the underlying causes so a careful history should be taken. The history includes specific symptoms such as itching, discharge, irritation, dysuria, dyspareunia, vaginal odor, rash, pain, and burning. Documenting the nature of the discharge including color, consistency, and quantity, as well as duration of the symptoms, prior treatments, and responses, along with mitigating or aggravating factors is important. Differentiating particular vulvar complaints from vaginal complaints is helpful.

4 Physical Examination

Inspection of the vulva may reveal areas of erythema, edema, excoriation of vulvar skin, ulceration, skin changes, color changes, rashes, raised lesions, or chronic vulvar skin changes. Vulvar tenderness can be elicited by manual palpation or by using a cotton-tip applicator. The vagina and cervix should be thoroughly inspected using a speculum. Samples can be obtained from the lateral vaginal wall or vaginal fornix for laboratory evaluation. These evaluations include:

- Vaginal pH.
- Fungal cultures.
- Smears for microscopic examination to identify trichomonads, clue cells, as well as presence of white blood cells or bacteria. A ratio of white blood cells to epithelial cells of more than 1:1 indicates an underlying infection, so further sexually transmitted infection screening should be performed in wet-mount/amine (whiff) test. A drop of 10% potassium hydroxide (KOH 10%), which is alkaline, is added to the vaginal secretions. The epithelial cells undergo lysis which increases the ability to identify hyphae or blastospores. Anaerobic bacteria produce amines. Adding 10 % KOH results in volatilization of the amines causing a sharp fishy odor.
- Biopsy of abnormal vulvar lesions may identify vulvar cancer, vulvar intraepithelial neoplasia, lichen sclerosus, vulvar dermatoses, and other conditions.
- Herpes culture should be performed in patients with vulvar or vaginal ulcerations.

5 Vulvovaginal Candidiasis

Vulvovaginal candidiasis is caused by an overgrowth of yeasts and is very common as 75 % of all women will develop a yeast infection in their lifetime (Faro et al. 1997). There is a peak of yeast infections during pregnancy when the vagina is exposed to high levels of estrogen (Sobel et al. 1998). Rarely vulvar candidiasis is present without concomitant vaginal candidiasis. *Candida albicans* is responsible in up to 90 % of cases with non-albican species making up the remainder (Sobel et al. 1998).

Recurrent vulvovaginal candidiasis (RVVC) occurs in less than 5% of women (Nyirjesy 2001). It is defined as four or more symptomatic *proven* episodes in 1 year (Sobel et al. 1998). Predisposing factors to RVVC are antibiotic use, corticosteroid use, diabetes, high sugar intake, high estrogen contraception, and deficiency in the immune system (such as women affected with human immunodeficiency virus) (Goswami et al. 2000; Duerr et al. 2003).

After treatment some women remain colonized with small number of yeast, and particularly if they have risk factors, they may have a new clinical episode of vulvovaginal candidiasis that is not from a reinfection (Vazquez et al. 1994). Extended length of treatment is often recommended due to the fact that while the yeast hyphae can be

eliminated by anti-yeast medications, the spores are resistant and will not be affected by the medicine until they hatch. Up to 33% of recurrent infections are caused by non-albican species such as *Candida glabrata*, *Candida parapsilosis*, *and Saccharomyces cerevisiae* (Nyirjesy et al. 1995).

Diagnosis Women present with symptoms of burning and irritation, vulvar pain, itching, dyspareunia, and vaginal discharge. On examination the white vaginal discharge is curd-like [cottage cheese], thick, and white. The vulva is erythematous and there may be labial swelling.

A wet-mount preparation usually reveals the hyphae and spores of *Candida albicans.* The branching, budding, and hyphal cell walls are easily visualized. However, the spores of *Candida glabrata* are more difficult to identify. They are spherical or ovoid and more variable in size but smaller than red blood cells. They are often clustered in groups and are associated with hyphal filaments. 10% KOH of lyse red and white blood cells reveal spores not otherwise seen on saline preparation.

Gram stain will show *Candida* spores as gram positive and the filaments as uniformly gram positive or with large gram-positive granules. In recurrent VVC cultures should be taken to accurately identify the species of candida. Detection can take up to a month. Sugar fermentation reactions are the most reliable for differentiating between species (Haefner 1999).

Treatment 10–20 % of women are colonized with candida (Sobel et al. 1998) and so treatment is only required in the context of symptoms. Women with RVVC should be reviewed to identify an underlying chronic illness affecting the underlying metabolic and immunological state (e.g., diabetes, systemic lupus erythematous, thyroid dysfunction). Controlling underlying medical conditions may minimize exogenous factors. Lowering the estrogen dose in combination with oral contraceptive pills may also be beneficial for women with RVVC. Modification of a high sugar intake may also be helpful.

A suppression and maintenance regime may be considered such as fluconazole capsule 150 mg every 72 h for three doses followed by fluconazole capsule 150 mg once a week for up to 6 months (this regime is not advised in pregnancy or breastfeeding). For some recurrent cases, concomitant treatment for BV as discussed below can be considered. Approximately 90 % of women will remain disease-free at 6 months and 40 % at 1 year (BASHH 2007).

Alternative regimes are:

- Topical imidazole therapy for 10–14 days according to symptomatic response followed by:
  - Clotrimazole pessary 500 mg once a week
  - Fluconazole capsule 50 mg daily
  - Itraconazole capsule 50–100 mg daily
  - Ketoconazole capsule 100 mg daily (BASHH 2007)

There may be inherent differences between *C. albicans* and non-*C. albicans* infections; therefore, obtaining a positive fungal culture, which includes identifying the infecting organism, is an essential first step in the management of RVVC. In RVVC secondary to *C. albicans*, resistance to antifungal therapy seems rare in that the vast majority of patients will, at a minimum, do well while on antifungal maintenance regimens. However, for infections caused by non-*C. albicans* species, particularly those due to *C. glabrata*, clinically evident resistance seems more common (Nyirjesy et al. 1995).

High-dose combined oral contraceptive pills are associated with increases in VVC infection. Affected women can consider swapping to a lower-dose combined preparation or an alternative non-estrogen-containing method of contraception. Low-dose combined oral contraceptives are unlikely to contribute to candida infections, so discontinuing their use is not recommended but could be considered in resistant recurrent cases. Copper intrauterine contraceptive devices have been identified as a possible risk factor as it has been shown that yeasts can adhere to the devices for recurrent VVC. Therefore women could

consider changing to an alternative method of contraception. Progesterone injectables may reduce women's predisposition to VVC due to the relative hypoestrogenic state and anovulation. Women with male partners should be warned that some vaginal and vulvar treatments for VVC can damage and weaken latex condoms (FRSRHC 2012).

The majority partners of women with recurrent VVC have negative cultures for candida (O'Connor and Sobel 1986) and so they are unlikely the source of reinfection. Treating the partners of women with RVVC does not reduce the risk of recurrence (Fong 1992) and is not recommended (FSRHC 2012).

Pregnant women are at high risk of VVC especially in the third trimester. The vaginal environment, under the influence of increased reproductive hormone levels, is conducive to yeast growth. Vaginal glycogen content increases, providing an abundant source of carbon for growth, adherence, and germination of candida. There is no evidence that VVC has an adverse effect on the pregnancy. Oral antifungals should be avoided. Women should be treated with topical imidazoles (FSRHC 2012).

6 Bacterial Vaginosis

Bacterial vaginosis (BV) is the commonest cause of abnormal vaginal discharge in women of reproductive age.

BV is characterized by an overgrowth of anaerobic bacteria in concentrations up to thousands of times greater than normal. Conventional culture techniques have identified *Gardnerella vaginalis*, *Prevotella* spp., *Mycoplasma hominis*, and *Mobiluncus* spp. as those most commonly found. *Gardnerella vaginalis* presence alone is not diagnostic as it can be a vaginal commensal in up to 50% of asymptomatic women (BASHH 2012). However its role in forming a biofilm with other bacteria may be key to the etiology of BV (Swidsinski et al. 2005). Molecular techniques have identified the presence of other species of bacteria including *Atopobium vaginalis*, *Clostridiales* spp., *Leptotrichia* spp., and *Sneathia* spp. (Fredricks et al. 2005).

BV is sexually associated as opposed to sexually transmitted. It is linked with sexual behaviors including sexual, oral, and digital intercourse (Fethers et al. 2008). BV has not been found in women who are truly sexually inexperienced (Fethers et al. 2005). Other risk factors include vaginal douching, recent change of sex partner, multiple sexual partners, smoking, presence of a sexually transmitted disease, and copper intrauterine contraceptive device (Klatt et al. 2010). There is debate about whether BV is merely an imbalance in vaginal ecology or is initiated as a sexually transmitted infection.

The presence of BV increases the risk of preterm birth with low birth weight by 40 %.

Diagnosis At least three of the four following criteria must be present to diagnose BV by Amsel's criteria (Amsel et al. 1983): (1) thin, white, homogeneous discharge which looks like skimmed milk that can be adherent to vaginal walls, (2) clue cells on wet-mount microscopic examination, (3) pH of vaginal fluid >4.5, and (4) positive whiff test – release of a fishy odor on adding alkali (10% KOH).

If a gram-stained vaginal smear is taken, BASHH recommends evaluating this by the Hay/Ison criteria (Ison and Hay 2002). Hay/Ison criteria are defined as follows: grade 1 (normal), *Lactobacillus* morphotypes predominating; grade 2 (intermediate), mixed flora with some *Lactobacilli* present, but *Gardnerella* or *Mobiluncus* morphotypes also present; and grade 3 (BV), predominantly *Gardnerella* and/or *Mobiluncus* morphotypes, few or absent *Lactobacilli*. BV is caused by a complex change in normal vaginal bacterial flora making a vaginal culture generally useless. Additionally, *G. vaginalis* can be cultured in up to 50–60 % of asymptomatic, healthy women. The Affirm VP III [DNA probe] test can detect high concentration of *G. vaginalis*.

Treatment Most patients will initially respond to pharmacological treatments to BV; however,

recurrence is common with more than half recurring by 12 months (Bradshaw et al. 2006). Metronidazole or clindamycin administered either vaginally or orally results in 70–80% of cure rates. Tinidazole 2 g once daily for 2 days or 1 g once daily for 5 days has been approved for treatment of bacterial vaginosis.

Options for treatment of recurrent bacterial vaginosis include suppressive treatment with metronidazole vaginal gel used twice a week, oral antibiotics followed by boric acid, and then suppressive therapy with metronidazole vaginal gel. Probiotic therapy may be considered but optimal treatment has not been established. Acidifying gels [boric acid] may be effective (FSRHC 2012).

Women using a copper intrauterine contraceptive device may consider changing to an alternative method of contraception (FSRHC 2012). Oral combined contraceptive pills and condoms are associated with a reduced risk of BV (Calzolari et al. 2000).

Symptomatic pregnant women should be treated in the usual way. Women with BV with additional risk factors for preterm birth may benefit from treatment before 20 weeks of gestation, and therefore screening such high-risk groups should be considered. Treatment of choice is metronidazole and is not associated with teratogenicity (BASHH 2012). Metronidazole alters the taste of breast milk, so breastfeeding mothers should receive clindamycin or be advised to stop feeding during the course and for 24 h after.

7 Trichomonas vaginalis

*Trichomonas vaginalis (*TV*)* is a flagellated anaerobic protozoan. It is rarer than RVVC and BV. It is sexually transmitted. TV can increase the risk of getting or spreading other sexually transmitted infections including HIV.

Diagnosis Up to 50% of women are asymptomatic with a third becoming symptomatic within 6 months. Those with symptoms complain of vaginal and vulvar discomfort, characteristically soreness or burning, dyspareunia, and vaginal discharge. Occasionally women complain of abdominal pain or vulvar ulceration. The typical vaginal discharge described as copious yellow green, frothy, and foul smelling only occurs in up to 30% of women. The discharge can range from thin and scanty to profuse and thick (Fouts and Kraus 1980; Wolner-Hanssen et al. 1989). On examination the cervix may have the classic "strawberry appearance" as a result of punctate cervical microhemorrhages. This can be seen by the naked eye but more commonly picked up at colposcopy (Fouts and Kraus 1980; Wolner-Hanssen et al. 1989). Vaginal pH is generally greater than 5.0 and often greater than 6.0. *T. vaginalis* may be seen on Papanicolaou smears.

Trichomonads are seen by a light field microscopy of the vaginal discharge on wet mount. Vaginal discharge is collected and mixed with saline on a glass slide and a coverslip is placed on top. The wet preparation slide should be scanned at both low and high magnification to confirm trichomonads [oval- or pear-shaped protozoans with a flagella] and to visualize the flagella. The slide must be read in under 10 min as trichomonads quickly lose their motility and after this time are more difficult to identify (Kingston et al. 2003). Microscopy can be performed in a clinic setting, near to the patient.

Point of care tests are available [such as rapid antigen tests and nucleic acid amplification] that do not require instrumentation. They can provide a result in 30 min and so can be performed in the clinic setting near the patient. It is a suitable alternative to culture or molecular testing. These tests have a high sensitivity (greater than microscopy) and specificity (Nye et al. 2009).

In difficult-to-diagnose cases, culture of TV or nucleic acid amplification tests could be considered as they have a higher sensitivity compared to microscopy (BASHH 2014a). Several culture mediums are available. Specimens should be incubated anaerobically and growth detected in 48 h.

Treatment *T. vaginalis* is a multifocal infection of the vaginal epithelium. Vaginal epithelium, Skene's glands, Bartholin's glands, and urethra

can all be affected, so systemic treatment is essential for complete cure. Nitroimidazole drugs [metronidazole] given in either single dose or over a prolonged period result in cure in over 90% of cases (Forna and Gulmezoglu 2003).Therefore recommended regimes are metronidazole 2 gm orally in a single dose or metronidazole 400–500 mg twice daily for 5–7 days (BASHH 2014a).

Recurrent TV can be due to drug resistance but is more commonly due to reinfection due to failure to treat all sexual partners or a new sexual contact. Therefore it is important to reconfirm the diagnosis in patients who return with recurrence of symptoms. Partner notification is required and all parties treated. To best achieve this, sexual health services should be involved. Patients should be advised to avoid sexual contact for at least a week and until their partners have completed treatment and follow-up (BASHH 2014a).

A strain of *T. vaginalis* exists that is resistant to metronidazole and other nitroimidazoles (Kirkcaldy et al. 2012). Therefore for patients that continue to have *T. vaginalis* despite therapy and in which reinfection is excluded, increased doses and longer duration of therapy may be required. Regimes include metronidazole or tinidazole 2 gm a day for 5–7 days (BASHH 2014a). In women who continue to not respond, resistance testing should be considered. Treatment protocols guided by resistance testing results have improved outcome (Bosserman et al. 2011). For women with recurrent symptoms, a test of cure is then recommended (BASHH 2014a). Concomitant treatment with an antifungal can also be considered.

8 Threadworms

Threadworms are nematode infection with *Enterobius vermicularis*. It is also known as pinworm or enterobiasis. It is the most common helminthic infection in the United Kingdom. It is most commonly seen in children aged 5–9 years but can affect any age, frequently affecting family groups or institutions. Overcrowding and poor hygiene contribute to spread and reinfection.

The female threadworm is 1 cm long and a little under 1 mm in diameter. It is white and pointed at each end. The male threadworm is much smaller at only 4 mm long and is rarely seen. Female threadworms may be seen at night emerging from the anus to lay eggs. The female lays on average over 10,000 eggs outside around the anus, vagina, and urethra. The eggs are so small that they are invisible to the naked eye and are accompanied by an irritant mucus, which causes intense itching and scratching. Scratching transmits the eggs from the perineal and perianal skin to the hands. Then these are transmitted to the mouth, swallowed or inhaled, and then ingested. The larvae hatch in the small intestine and migrate to the colon where they reach maturity over 2 weeks. Adult worms live for up to 6 weeks. Its only host is humans (Ibarra 2001). Transmission may occur through handling of contaminated food, clothing, and bed linen.

Diagnosis Women present with itching of the vulva or anus, especially at night. Itching can cause loss of sleep. Threadworms do not move much and so can be easily missed, but if seen are diagnostic. Eggs can be detected by the adhesive tape test. Transparent wide hypoallergenic adhesive tape is applied to the perianal skin first thing in the morning, before wiping or bathing. It does not have to be left on overnight. The tape is then examined microscopically and the eggs are seen adherent to the tape.

Treatment Mebendazole kills the threadworms. It is administered as a single oral dose and is best repeated after 2–3 weeks in case reinfection has occurred. Other possible drugs include albendazole and pyrantel pamoate. Asymptomatic infections can occur and so all the family and close contacts should be treated at the same time, regardless of symptoms.

Drug treatment is not mandatory. The life cycle of threadworms is 6 weeks and the eggs remain viable for further 2 weeks. Excellent hygiene over this time frame will lead to the threadworms dying

out without a chance to reinfect. Hygiene measures include:

- Wash each morning especially around the anus and vulva.
- Keep fingernails short and clean.
- Wash hands and scrub under the nails first thing in the morning. Wash hands and nails prior to preparing food and eating.
- Wash hands and nails after using the toilet.
- Put toothbrushes in a closed cupboard and rinse them well before use.
- Do not share towels or beds. If possible wash towels and bed linen daily.
- Change and wash underwear and nightwear daily.
- Do not shake the laundry as this can spread eggs.

9 Atrophic Vaginitis

The storage of glycogen by the vaginal epithelium is under the influence of estrogen. If women have extremely low endogenous estrogen production such as after the menopause or bilateral salpingo-oophorectomy, gonadotrophin-releasing hormone analogues, radiation, chemotherapy, or immunological disorders, the glycogen content of the vaginal epithelium drops resulting in atrophy (Summers et al. 2007). It has been estimated that up to 50 % of women experience symptoms due to atrophic vaginitis at 5 years postmenopause (Sturdee and Panay 2010). Postpartum women can also experience atrophy because of the decline in estrogen levels in conjunction with the loss of placental estrogen, and prolactin produced during lactation has an antagonistic effect on estrogen.

Reduced endogenous estrogen reduces the glycogen content of the epithelium which in turn reduces lactic acid production and increases the vaginal pH leading to a reduction in *Lactobacillus*.

Diagnosis History and physical examination will usually lead to a diagnosis. Symptoms of atrophic vaginitis include soreness, postcoital burning, dyspareunia, dryness, vulvar or vaginal itching, leucorrhea, pressure, yellow discharge, and occasional spotting. There are often associated urinary tract symptoms such as dysuria, frequency, leaking, and infection. The vaginal epithelium appears thin, smooth, pale, or shiny. The vaginal rugae will have disappeared. Petechiae and increased friability or erythema may be present. There can be fusion of the labia minora, introital stenosis, thin vulvar skin with patch erythema, or discolored lesions. Vaginal pH will be raised and a wet mount shows white blood cells and a lack of *Lactobacillus* (Kingston 2009).

Treatment Many women with vaginal atrophy are not symptomatic, so treatment may not be desired. For symptomatic women treatment with vaginal estrogens is effective. Tablets and creams can be used nightly for 2 weeks and then twice weekly. Twice weekly maintenance dose can be continued long term and should be continued for as long as women have distressing symptoms. Systemic absorption is minimal and so progesterone is not required (BMS 2016). Some women may prefer to switch to oral or patch therapy after a few weeks or months of vaginal treatment. Those patients presenting with symptoms while already taking systemic HRT may show improvement in symptoms with the addition of vaginal estrogens (NICE 2015).

10 Lichen Sclerosus

Lichen sclerosus (LS) is an inflammatory dermatosis of unknown etiology. It is a chronic relapsing disease. There is evidence to suggest that autoimmune factors may be involved in its pathogenesis, and recent evidence has shown autoantibodies to extracellular matrix protein 1 (Oyama et al. 2003). There is an increased frequency of other autoimmune disorders in females with lichen sclerosus (Meyrick-Thomas et al. 1988).

Diagnosis Presentation is usually with intense vulvar itching, but soreness, burning, or pain may be the primary symptom, particularly where

there has been chronic itch. Pruritus is often worse at night and many women have disturbed sleep. If the introitus has narrowed, they may disclose dyspareunia and sexual dysfunction.

On examination LS classically appears as porcelain-white plaques on the vulva, perineum, and perianal skin. The texture of "parchment" or "cigarette paper" skin is characteristic and helps to distinguish lichen sclerosus from lichen planus or vitiligo. Changes may be localized or distributed in a "figure of eight" around the perianal skin figure involving the labia minora and majora, vestibule, clitoral hood, and perineum. Other features include fissuring, hyperkeratosis, and erosions. Loss of architecture may be manifest as loss of the labia minora and/or midline fusion. The clitoral hood may be sealed over the clitoris so that it is buried or a clitoral pseudocyst may have formed. The vagina and cervix are spared, but extragenital lesions can be seen in around 10 % of cases.

Clinical diagnosis of lichen sclerosus is accepted as standard practice (Neill et al. 2002). Outpatient biopsy under local anesthesia is well tolerated. Histology shows epidermis thinning with subepidermal hyalinization and deeper inflammatory infiltrate. It is useful in diagnostically difficult cases, those which fail to respond to treatment and suspicious areas. The lifetime risk of squamous cell carcinoma (SCC) in cases of lichen sclerosus is less than 5 % (BASSH 2014b), and this may be higher than actual risk owing to the probable high prevalence of undiagnosed lichen sclerosus (Neill et al. 2002).

Investigation for autoimmune disease should be considered, especially thyroid dysfunction (i.e., T4 and TSH) as it is often asymptomatic.

Treatment Women are treated symptomatically. Recommended treatment is by ultrapotent topical steroids, e.g., clobetasol propionate. Various regimens are used with no evidence of an optimal regime (BASSH 2014b). One of the most common regimes is to use the treatment daily for one month, then alternate days for one month, then twice weekly for one month, followed by reviewing the patient after the three months. It can then be used as needed depending on symptoms (Neill et al. 2002). Ointment bases are much better to use on the anogenital skin because of the reduced need for preservatives in an ointment base and hence less risk of a secondary contact allergy (BASHH 2014b). Topical steroids are safe to use while pregnant or breastfeeding.

Women with active LS should have dermatology involvement. Those with complex conditions, such as developed vulvar intraepithelial neoplasia (VIN) or SCC on a background of LS, should be seen and followed up by an experienced clinician or in a specialized vulvar clinic. Surgery should only be used for the treatment of coexistenting abnormality requiring excision or to release labial fusion. Disease tends to recur around the scars (BASSH 2014b).

Patients should be informed about the condition and given written information. Women must be made aware of the small risk of neoplastic change. They should be advised to contact the doctor if they notice a change in appearance or texture (e.g., lump or hardening of the skin), or if there is a major change in symptoms. Good vulvar hygiene may be helpful.

11 Lichen Planus

Lichen planus (LP) is a rare inflammatory disorder of unknown but probably autoimmune pathogenesis. It has manifestations on the skin, genital and oral mucous membranes, and more rarely the lacrimal duct, esophagus, and external auditory meatus. It affects 1 % of women.

Diagnosis Vulvar LP presents with intense itching, pain, soreness, dyspareunia, and bleeding. A purulent discharge caused by desquamative vaginitis is common when the vagina is involved (Goldstein and Metz 2005). The heterogenous appearance can be divided into three groups:

- Erosive LP is the most common subtype to cause vulvar symptoms. The mucosal surfaces are eroded looking "red raw"; the edges of the erosions are mauve. The lesions consist of friable telangiectasia with patchy erythema

which are responsible for the common symptoms of postcoital bleeding, dyspareunia, and a variable discharge which is often serosanguinous. As erosions heal synechiae and scarring can develop, therefore vaginal lesions should be recognized and treated early to prevent scarring, stenosis, and introital narrowing (Genadry and Provost 2006). This type is also seen in the oral mucosa although synechiae are uncommon. Wickham striae are pathognomonic. On the vulva they appear as white reticular or linear papules and they may also be found on the buccal mucosa of the mouth. Vulvovaginal gingival syndrome describes erosive disease occurring in the vulva, vagina, and mouth.

- Classical LP usually presents well-circumscribed papules which are flat topped. They are found on the trunk, extremities, and the keratinized anogenital and vulvar skin, with or without striae. Hyperpigmentation frequently follows their resolution, particularly those with dark skin. This type of lichen planus may be asymptomatic.
- Hypertrophic LP is relatively rare and can be difficult to diagnose. Lesions particularly affect the perineum and perianal area, presenting as thickened warty plaques which may become ulcerated, infected, and painful. Because of these features, they can mimic malignancy. They do not appear to be accompanied by vaginal lesions.

Skin changes elsewhere can be helpful to aid diagnosis. Histology of a vulvar biopsy is diagnostic and shows irregular saw-toothed acanthosis, increased granular layer and basal cell liquefaction, and band-like dermal infiltrate which is mainly lymphocytic (BASSH 2014b). Biopsy is essential if diagnosis is uncertain or to exclude coexisiting VIN or SCC. The incidence of developing SCC is as high as 3 % (Cooper and Wojnarwowska 2006).

Treatment Good vulvar care (see below) should be recommended. Potent or ultrapotent topical steroids constitute first-line treatment and suppositories can be used for vaginal disease. Daily application for up to 3 months has been advocated, reducing as required (Goldstein). However there is not an evidence-based optimal regime. Maintenance can be achieved by either regular application of a weaker steroid or less frequent use of a potent steroid. Delivery of corticosteroids to the vagina is a challenge. A proprietary preparation containing hydrocortisone (Colifoam) is introduced with an applicator. Prednisolone suppositories may be used in more severe cases (BASHH 2014b). There is not any good evidence in systemic therapy. Vaginal dilators should be used early in vaginal involvement to prevent adhesions and topical local anesthetic gel can help with discomfort.

Surgery is reserved for reversal of severe scarring, particularly for younger or sexually active women.

Lichen planus is very often misdiagnosed as lichen sclerosus because of similarities in the presentation and the presence of white plaques. However, vaginal involvement precludes lichen sclerosus as a diagnosis. Lichen sclerosus and lichen planus are thought to be present simultaneously in some cases, perhaps those with more resistant disease (Neill et al. 2002). Referral to a multidisciplinary vulvar clinic should be considered for any woman with erosive disease, coexisting diseases, intractable symptoms, or scarring complications.

12 Contact Dermatitis

Contact dermatitis resulting in inflammation commonly affects the vulva. Inflammation of the skin occurs after exposure to an allergen (allergic dermatitis) or an irritant (irritant dermatitis).

Allergic reactions are a cell-mediated (type 4) immunological response that occurs on reexposure after an initial sensitizing episode. The history of symptoms may reveal the diagnosis. Patch testing can be performed to determine the allergen among women in ongoing symptoms. Common allergens include nail polish, latex preservatives, and lanolin. There are also reports of semen rarely causing symptoms, and absence of

symptoms following intercourse with a condom may lead to a suspicion of this.

Irritant-induced contact dermatitis can be acute or chronic. It may occur from acute exposure to a potent irritant or after repeated exposure to a weak irritant. The postmenopausal vulva is particularly susceptible to irritation. Possible irritants include detergent, panty liners, moisturizers, chronic wetness from vaginal discharge or urine, topical medications, antifungals, latex, lubricants, spermicides, cosmetics, fragrances, cleansing products, and washing powders/liquids (Kingston 2009).

Diagnosis A history of itching is the most common symptom. However, a potent stimulant causing acute reactions involving the mucosa can cause symptoms of burning, rawness, and pain. Persistent scratching in chronic conditions will also frequently lead to pain. On examination the skin can be red and edematous with exudation and weeping and rarely erosions and ulcers. If the exposure to the stimulant is prolonged, then lichenification, scaling, and thickening of the skin can occur with fissuring (see lichen simplex chronicus below).

Treatment Where possible, identify and remove the exacerbating agent. Provide women with written information on good vulvar care (see below). Aqueous cream has been shown to be a potential irritant when it is used as an emollient, so it's recommended as a soap substitute only. Consider topical corticosteroids in ointments for 7–10 days to treat the inflammation. In severe, rare cases, oral steroids could be considered. Any superimposed infection may need treating with antibiotics or antifungals as appropriate (Kingston 2009).

13 Lichen Simplex Chronicus

Lichen simplex chronicus results from an itch-scratch-itch cycle caused by another pathology making LSC a secondary condition. The original itch can be triggered by (BASHH 2014b):

- Underlying dermatosis – atopic dermatitis and superficial fungal (tinea and candidiasis) infections
- Environmental factors causing irritant or allergic dermatitis
- Systemic illness – obstructive biliary disease (primary biliary cirrhosis and primary sclerosing cholangitis), renal failure, hyper- or hypothyroidism, Hodgkin's lymphoma, and polycythemia rubra vera
- Psychiatric disorders – obsessive-compulsive disorder, anxiety, depression, and dissociative experiences

Diagnosis Patients characteristically describe an intractable itching and scratching, especially during sleep at night. Examination reveals lichenification, i.e., thickened, slightly scaly, pale, or earthy-colored skin, exaggerated skin markings, and excoriations, maybe more obvious on the side opposite the dominant hand. There may be erosions and fissuring. Pubic hair can be lost as a result of scratching (BASHH 2014b).

Treatment To treat the women, the cycle must be broken by treating the underlying cause, if known, and good vulvar care. Use a soap substitute for all washing and an emollient regularly. Emphasizing daily drying techniques may be helpful. If needed sedating antihistamines at night can be used to reduce the itch and aid sleep (such as hydroxyzine). Potent or ultrapotent topical corticosteroids can reduce the inflammation and treat the lichenification. These should be in ointment form as creams can cause irritation. Secondary infection is possible and so must be screened for and treated, if present, with an antifungal or antibiotic as necessary. Cognitive behavioral therapy may be helpful if there are coexisting mental health issues (BASHH 2014a).

14 Vulvar Care

Women who are prone to symptoms may benefit from the following advice on personal hygiene:

Table 1 Summary of vulvovaginitis

	Vulvovaginal candidiasis	Bacterial vaginosis	*Trichomonas vaginalis*	Threadworms	Atrophic vaginitis	Contact dermatitis	Lichen sclerosus	Lichen planus	Lichen simplex chronicus
Discharge	Thick white curd-like	Thin adherent to walls, white/gray	Scanty to profuse, frothy yellow	Normal	Normal	Normal	Normal	Normal	Normal
Odor	Nil	Fishy offensive	Fishy	Nil	Nil	Nil	Nil	Nil	Nil
Itch	Present	Nil	Present	Present worse at night	Nil	Present	Present predominately at night	Present predominately at night	Present (characteristic)
Other symptoms	Dyspareunia, burning	Nil	Vaginal and vulvar discomfort, burning, dyspareunia	Vaginal and vulvar discomfort, burning, dyspareunia	Burning, dyspareunia, postmenopausal bleeding	Irritation, burning,	Vaginal and vulvar discomfort, burning, dyspareunia	Vaginal and vulvar discomfort, burning, dyspareunia	Nighttime scratching
Visible Signs	Erythema, edema, satellite lesions	Nil	Vulvitis, vaginitis, cervicitis, "strawberry cervix"	Worms may be seen Eggs can be collected on adhesive tape	Thin epithelium, loss of rugae, pale, petechiae	Erythema of vulva	White plaques and "parchment" skin. In a figure-of-eight distribution		Vulvar lichenification, excoriation
Vaginal pH	<4.5	>4.5	>4.5 typically 5–6	<4.5	>4.5	<4.5	<4.5	<4.5	<4.5
Cause	Yeasts	Reduced lactobacilli with overgrowth of anaerobic species	Trichomonads	Nematode infection	Reduced estrogen	Environmental factors	Underlying condition itch-scratch-itch cycle	Unknown inflammatory condition	Unknown likely autoimmune
Treatment	Antifungals, vulvar care	Metronidazole	Systemic antibiotics	Mebendazole	Vaginal estrogens, vulvar care	Remove factor, steroids, vulvar care	Treat underlying condition, steroids, vulvar care	Ultrapotent topical steroids	Ultrapotent topical steroids

- Keep genital area dry (moisture encourages growth of candida and may cause chronic skin irritation).
- Wear 100 % cotton underwear, avoid synthetic materials, and wear loose fitting clothing.
- Use cool baths to help to soothe the skin, but do not wash excessively.
- Do not wear panty liners or change them often.
- Do not use soaps, perfumes, or detergents on the vulva, including feminine hygiene or wet wipes. Instead use a soap substitute. Shampoo hair over a basin separate from bath and shower.
- Avoid frequent or prolonged use of hot tubs.

With regard to treatment, when topical steroids are used in addition to an emollient, then the emollient should be used first and the steroid 15 min later. This moisturizes the skin and prevents spread of the steroid onto normal skin. Women should be reassured that atrophy is rare with short-term use of potent corticosteroids.

15 Emotional Care

Patients should be given a detailed explanation of their condition with details of any long-term implications for their own health and that of their partners. They should be offered written information and directed to further resources, such as online websites and/or patient support. Recurrent vulvovaginitis can affect patients psychologically. They are often frustrated and feel despair. The symptoms may have an effect on their sexual relationships and personal relationships.

16 Summary

Vulvovaginitis is the most common reason why women present to a gynecologist. The term covers inflammation or infection of the vagina and/or vulva. Women with symptoms lasting for more than 6 months experience chronic vulvovaginitis. Clinical presentation of women with vulvovaginitis is similar regardless of the underlying cause and so a careful history should be taken. Symptoms include itching, discharge, irritation, dysuria, vaginal odor, rash, and burning. Signs include erythema, edema and excoriation of vulvar skin, ulceration, or chronic vulvar skin changes. The following investigations can aid diagnosis, vaginal pH, amine whiff test, vulvar biopsy, fungal cultures, and wet smears. The commonest causes, their presentation, and the treatment are summarized in Table 1.

17 Conclusion

Obtaining an accurate history from women, with vaginal vulvar symptoms, is critical in diagnosing vulvovaginitis. The results of physical examination and investigation will in turn lead to the underlying cause and therefore determine correct treatment. All women will benefit from good vulvar skin care [clean and dry] and emotional support.

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Pelvic Inflammatory Disease and Other Upper Genital Infections

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Contents

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Abstract

Pelvic inflammatory disease (PID) refers to an acute or subclinical infection of the female upper genital tract and can be further classified by the anatomic structures affected. It is caused by an ascending infection to the uterus, fallopian tubes, ovaries, and pelvic cavity. The most common inciting pathogens are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, though PID is considered and treated as a polymicrobial infection. PID should be considered in the differential diagnosis in women, especially reproductive age, who present with acute pelvic pain. Sexual activity is the most important risk factor for PID, and a thorough sexual history should be obtained. Barrier contraceptions are protective. PID is diagnosed clinically based on symptoms and pelvic exam. Testing for sexually transmitted infections should be performed and can aid in the diagnosis. A high index of suspicion should be used for diagnosis and early empiric treatment with antibiotics started to reduce sequelae caused by inflammatory scarring of the fallopian tubes. Specific antibiotic regimens have been recommended by the Centers for Disease Control and Prevention (CDC). Mild or moderate PID can be treated as an outpatient with close follow-up. Careful consideration should be made for inpatient admission in those who fail outpatient management and those with severe disease or tubo-ovarian abscess (TOA). Long-term sequelae include increased risk of ectopic pregnancy, infertility, and chronic pelvic pain.

Keywords

Pelvic inflammatory disease (PID) • Salpingitis • Pyosalpinx • Endometritis • Tubo-ovarian abscess (TOA) • *Fitz-Hugh-Curtis syndrome* • Upper genital infection • Sexually transmitted infection (STI) • Tubal factor infertility

1 Introduction and Epidemiology

Pelvic inflammatory disease (PID) is a clinical diagnosis and refers to an acute infection of the female upper genital tract including the uterus, fallopian tubes, and ovaries.

PID can be difficult to definitively diagnose, and a low threshold for treatment is recommended given the clinical sequelae of this infection.

As such, the exact number of women affected by PID is unknown. It is estimated that PID accounts for approximately 106,000 outpatient clinical visits and 60,000 hospitalizations and is a common reason for emergency department visits annually in the United States. Recently, the lifetime prevalence of treatment for PID has been decreasing from 8.6% in 1995 to 5.0% in 2006–2010 (CDC 2015a).

2 Anatomic Considerations

The diagnosis of PID is used to describe a spectrum of infection and inflammation within the female pelvic organs. Classically, PID involves infection of the fallopian tubes, also called acute salpingitis, though PID can affect the surrounding pelvic organs and can be further classified by the particular anatomy involved (Fig. 1).

3 Pathogenesis and Microbiology

PID is a polymicrobial infection, which results from bacteria (aerobic, facultative, and anaerobic) ascending from the vagina and cervix to the uterus, fallopian tubes, ovaries, and into the pelvic peritoneal cavity. While normal vaginal flora is important to maintaining vaginal health, the upper genital tract is a sterile environment. The endocervical canal serves as a barrier to maintain this sterile environment, protecting the upper reproductive organs from normal vagina flora as well as pathogenic bacteria. Disruption of this barrier can occur with cervical infection or cervicitis, menstrual bleeding, hormonal fluctuation, recent instrumentation, and possibly other factors which enable bacteria to ascend (Ross 2015).

Chlamydia trachomatis and *Neisseria gonorrhoeae* are the most common associated pathogens, particularly in young sexually active

- Endometritis: infection involving the endometrial cavity
- Salpingitis: infection involving the lumen of the fallopian tubes
- Pyosalpinx: presence of purulent material within the fallopian tubes
- Tubo-ovarian complex: agglutination of the fallopian tube and ovary (fallopian tube and ovary are distinct on pelvic imaging)
- Tubo-ovarian abscess (TOA): abscess formation involving fallopian tube and ovary (fallopian tube and ovary are not distinct on pelvic imaging)
- Pelvic Peritonitis: inflammation of the pelvic peritoneum, usually with pelvic free fluid
- Peri-hepatitis: inflammation of the liver capsule, also known as *Fitz-Hugh Curtis Syndrome*

Fig. 1 Upper genital infections, classified anatomically

women. Although testing of cervical swabs and pelvic abscess fluid in women with PID is not always positive for these organisms, it is believed that inflammation triggered by these pathogens plays a role in allowing other bacteria to ascend. Additionally, negative testing of cervical swabs for these pathogens does not rule out upper genital infection, so presumptive treatment is warranted. The initiating pathogen is not always identified, and empiric broad-spectrum antibiotics are used to treat the most likely mixture of pathogens (Fig. 2).

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Trichomonas vaginalis*
- *Gardnerella vaginalis*
- *Escherichia coli*
- *Bacteroides fragilis*
- *Streptococcus species*
- *Prevotella species*
- *Peptostreptococcus species*
- *Haemophilus influenzae*
- *Mycobacterium tuberculosis* (rare)
- *Actinomycosis* (rare, associated with IUD use)

Fig. 2 Pathogens implicated in PID

There have been conflicting studies regarding the significance of changes in the bacterial microenvironment associated with bacterial vaginosis (BV) as a risk factor for ascending pelvic infection. However, it is important to evaluate for BV in patients with suspected PID to guide treatment. Trichomonas vaginalis and vaginal anaerobes are also implicated in PID.

PID in postmenopausal women or those who are not sexually active is less likely to be related to sexually transmitted infection (STI). Other non-gynecologic pathogens can spread to the fallopian tubes by direct extension from inflammatory gastrointestinal disease, including appendicitis or diverticulitis, and rarely hematologic spread of pathogens including tuberculosis.

4 Risk Factors

Young premenopausal sexually active women are at highest risk for developing PID. The most important risk factor for PID is sexual activity,

- Younger age (< 25 years old)
- Sexually active
- Multiple or new sexual partners
- Young age at first intercourse
- Prior PID or STI
- Current infection with STI
- Sexual partner with STI
- Current or recent menstruation
- Recent endocervical or intrauterine instrumentation
- Douching
- Single status
- Lower socioeconomic status
- Substance abuse

Fig. 3 Risk factors

especially in women with multiple or new sexual partners. Additionally, breakdown of the endocervical protective barrier by menstrual bleeding, instrumentation, or active cervical infection are risk factors. Social factors have also been suggested (Fig. 3).

The link between risk of PID and birth control method has been studied, with inconclusive data regarding risk associated with oral contraceptive pills. There does not appear to be an increased risk of pelvic infection with the use of intrauterine devices; however, women may be at risk within

the first 3 weeks after insertion due to instrumentation (CDC 2013). Barrier contraception (i.e., condoms) has been shown to be protective against PID. Prior BTL may protect against progression of disease from proximal to distal fallopian tubes.

5 Clinical Manifestations

The most common clinical presentation of PID is the acute onset of bilateral lower abdominal or pelvic pain, usually presenting over the course of days. Additional symptoms include unusual foul-smelling vaginal discharge or abnormal vaginal bleeding. In severe disease, patients may complain of nausea, vomiting, diarrhea, or anorexia or may present with fevers, chills, tachycardia, or other signs of acute infection. Patients may also complain of menorrhagia, dysmenorrhea, or dyspareunia. Symptoms commonly occur during or shortly after menses. Symptoms may be subtle and may follow a more indolent course over weeks to months (Ross 2015). Additionally, some women are asymptomatic, and a retrospective diagnosis is made after finding evidence of tubal disease in the workup for infertility (Wiesenfeld et al. 2012).

5.1 History and Physical Exam

A detailed history should be elicited including characterization of acute pain symptoms, associated symptoms, review of systems including bowel and bladder function to exclude other etiologies, and sexual history.

Temperature and vital signs should be assessed to evaluate for signs of infection, systemic inflammatory response syndrome (SIRS), or sepsis. A complete physical exam should be performed.

On abdominal exam, the physician should assess for focal tenderness, rebound tenderness, guarding, abdominal distension, and abdominal or pelvic masses. Lower abdominal tenderness to palpation may be unilateral or bilateral. Rebound tenderness and decreased bowel sounds suggest peritonitis. Right upper quadrant pain may be seen in a patient with perihepatitis or *Fitz-Hugh-Curtis syndrome* caused by inflammation of the liver capsule.

On pelvic exam, the physician should assess for abnormal vaginal bleeding or discharge. Mucopurulent cervical discharge is highly suggestive of PID. Pelvic organ tenderness can be assessed on bimanual exam. Cervical motion tenderness (CMT) can be elicited on bimanual pelvic exam with the providers examining fingers in the posterior fornix moving the cervix anteriorly or laterally. This test is positive when the patient experiences significant pain upon movement of the cervix and suggests pelvic peritoneal inflammation. Cervical motion, uterine, and adnexal tenderness are characteristic findings indicative of PID on pelvic exam. Pelvic mass on exam may suggest TOA and should be further evaluated with pelvic imaging.

6 Diagnosing PID

There is no gold standard for the diagnosis of PID. Symptoms and findings can be mild and nonspecific, making definitive diagnosis difficult. Women with PID can also be asymptomatic. As such, PID is diagnosed clinically based on symptoms and pelvic exam. The CDC has suggested diagnostic criteria as guidelines to assist healthcare providers (Fig. 4).

If no cause other than PID can be identified, the presumptive diagnosis is made in sexually active young women or women at risk for sexually transmitted infections, who complain of pelvic or lower abdominal pain and have physical exam findings of pelvic organ tenderness on exam – cervical motion, uterine, or adnexal tenderness. Although these criteria will result some false positives (treatment of women who do not have PID), treatment is warranted to prevent the serious reproductive consequences of delayed treatment or untreated PID.

A physician should consider other possible diagnoses in the approach to a patient with acute pelvic pain. Figure 5 shows the differential diagnosis for abdominal and pelvic pain, including gynecologic and non-gynecologic etiologies.

Minimum Diagnostic Criteria
1. Pelvic pain or lower abdominal pain
2. Cervical motion tenderness (CMT) or adnexal tenderness or uterine tenderness

Additional Diagnostic Criteria (which support the diagnosis of PID)
1. Fever > 101°F or > 38.3°C
2. Abnormal cervical mucopurulent discharge or cervical friability
3. Presence of WBC on saline microscopy of vaginal fluid
4. Elevated inflammatory markers: C-reactive protein, Erythrocyte sedimentation rate
5. Microbiologic testing confirming diagnosis of cervical infection with *C. trachomatis* or *N. gonorrhoeae*

Most Specific Criteria (usually not necessary)
1. Endometrial biopsy with histopathologic evidence of endometritis
2. Pelvic imaging showing thickened fluid filled tubes, free fluid in the pelvis, or TOA
3. Laparoscopic abnormalities consistent with pelvic infection

Fig. 4 Diagnostic criteria recommended by the Centers for Disease Control and Prevention (CDC 2015b)

- Gynecologic:
  - PID
  - Ectopic pregnancy
  - Ovarian torsion
  - Ruptured ovarian cyst
  - Spontaneous abortion
  - Endometriosis
  - Degenerating fibroid(s)
- Non-gynecologic:
  - Appendicitis
  - Acute cystitis
  - Urolithiasis
  - Diverticulitis
  - Ulcerative colitis
  - Inflammatory bowel disease
  - Irritable bowel syndrome
  - Functional pain

Fig. 5 Differential diagnosis for abdominal or pelvic pain

7 Complications of PID

7.1 Perihepatitis or *Fitz-Hugh-Curtis Syndrome*

Fitz-Hugh-Curtis syndrome develops from inflammation of the peritoneal surface of the liver capsule in the anterior right upper quadrant and can occur in approximately 10% of women with acute PID. Women may complain of right upper quadrant pain or referred right shoulder pain and may have tenderness in this area on exam. The liver stroma is rarely involved, and liver enzymes are normal to mildly elevated. Adhesions noted intraoperatively suggest this diagnosis.

7.2 Tubo-ovarian Abscess

Purulent drainage from the infected fimbriae of the fallopian tube can lead to extension of infection to the ovary, with these structure forming an infected mass together. This mass is referred to as a tubo-ovarian complex when the fallopian tube and ovary are agglutinated, but still distinct on pelvic imaging and a tubo-ovarian abscess (TOA) when they are no longer distinct from one another on imaging. TOAs may also involve adjacent structures including the bowel, bladder, or the contralateral adnexa.

TOAs may also form due to spread of infection from surrounding structures, for example, as a result of appendicitis, diverticulitis, or inflammatory bowel disease, though the pathogenesis, microorganisms, and treatment will differ from TOAs caused by PID and sexually transmitted infection.

TOAs represent a severe form of PID (Beigi 2015). A minority of women with PID develop TOA, but this diagnosis should be suspected when a woman presents with a suspected pelvic mass or severe disease. Signs of severe disease include marked pain or tenderness, fevers, or other signs of systemic infection. TOAs require inpatient admission for broad-spectrum intravenous antibiotics. Additionally, abscess drainage may be required. TOAs can be life-threatening with the risk of abscess rupture, resulting in severe peritonitis and sepsis. Ruptured TOAs present with an acute abdomen and are a surgical emergency.

7.3 Long-Term Sequelae

Scarring and anatomic distortion caused by inflammation, particularly in the fallopian tubes, can lead to significant reproductive sequelae including chronic pelvic pain, infertility, and ectopic pregnancy (see section below on "Long-Term Complications").

8 Diagnostic Testing

All women with suspected PID should minimally be tested for pregnancy, vaginal infection by saline microscopy (wet mount), and sexually transmitted infections (STIs) including *N. gonorrhoeae*, *C. trachomatis*, and human immunodeficiency virus (HIV).

Empiric treatment should be started once a presumptive clinical diagnosis has been made and other emergent causes of pelvic pain have been excluded. Microbiologic testing should be performed prior to initiation of antibiotics, but treatment should be given regardless of results and should not be delayed pending results.

8.1 Pregnancy Test

Serum or urine beta-human chorionic gonadotropin (beta-HCG) should be drawn to evaluate for pregnancy, as pregnancy-related diagnoses (i.e., ectopic pregnancy, septic abortion) must be ruled out as the etiology of pelvic pain. PID in pregnancy is rare, but can occur during the first trimester prior to formation of the mucous plug and decidua which function as protective barriers from ascending infection. Pregnant patients with PID should be admitted and antibiotic regimen altered to avoid the teratogenic effects of doxycycline. Pregnant patients with PID have higher risk of preterm labor.

8.2 Other Laboratory Tests

Additional tests may support the diagnosis of PID, but have poor sensitivity and specificity. When elevated, these may help in determining the severity of disease and the response to treatment.

- Complete blood count: leukocytosis is usually only seen in severe disease.
- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR): markers of inflammation, nonspecific.
- Aminotransaminases: consider checking liver enzymes in patients with severe nausea/vomiting or right upper quadrant pain.

8.3 Microbiology

- Testing for *N. gonorrhoeae* and *C. trachomatis*, usually by cervical swab.
- Saline microscopy (or wet mount) to evaluate for BV, yeast, and trichomonas.
- Testing for additional STIs including HIV, syphilis, and hepatitis B.
- Gram stain and culture are usually not necessary.

8.4 Histopathology

- Endometrial biopsy is nonspecific and generally not recommended in the diagnosis of PID. Biopsy may show polymorphonuclear leukocytes (PMNs) in acute infection or plasma cells in chronic infection.

9 Pelvic Imaging

Pelvic imaging should be obtained in patients:

1. With a suspected pelvic mass or tubo-ovarian abscess
2. With significant pain or tenderness or signs of severe disease
3. With no or minimal improvement with antibiotic therapy
4. To determine feasibility of draining a pelvic abscess
5. To exclude other etiologies if the diagnosis is unclear

9.1 Pelvic Ultrasound

As in other areas of gynecology, pelvic ultrasound is the preferred method of imaging in a patient with suspected pelvic infection and to evaluate other gynecologic etiologies of pelvic pain. During an acute infection, anatomy may appear normal on imaging. Pelvic ultrasound may reveal nonspecific findings suggestive of infection, including pelvic free fluid or tissue thickening of the endometrium, ovaries, and/or fallopian tubes (Hoffman et al. 2012).

- Pelvic Inflammatory Disease: The most specific findings of PID are thickened fluid-filled fallopian tubes. The tubal wall may become thickened >5 mm with apparent septations caused by folding of the tube. The tubes appear dilated and filled with fluid, debris, and rarely gas. In cross section, the tube may appear as a *cogwheel sign*. Doppler studies may show increased blood flow to the fallopian tubes.
- Tubo-ovarian Abscess: On imaging, TOA may be seen as a complex multilocular adnexal or cul-de-sac mass with thickened irregular walls, mixed echogenicity, and with septations, internal echos, or fluid levels. The normal adnexal architecture is often distorted, and in TOA, the ovary and fallopian tube cannot be distinguished from one another.

9.2 Additional Imaging

Computed tomography (CT) may be necessary for further diagnostic information, particularly in women where gastrointestinal tract disease (i.e., appendicitis) must be excluded or in a woman with a pelvic mass concerning for malignancy. Compared to pelvic ultrasound, CT imaging is more expensive and exposes the patient to radiation.

10 Treatment

Once the presumptive diagnosis of PID has been made, empiric treatment should be initiated (Ness et al. 2002). Broad-spectrum antibiotics are used to cover the likely implicated pathogens. The following recommendations have been made by the Centers for Disease Control and Prevention (CDC 2015b).

10.1 Outpatient Management

10.1.1 Criteria for Outpatient Management

Women with mild or moderate PID can usually be managed as an outpatient and treated with intramuscular and oral antibiotics. Recommended oral and intramuscular antibiotic regimens are shown in Table 1. Outpatient treatment requires that patients return in 2–3 days for a "PID check," which includes a repeat pelvic exam. If a patient is not reliably able to follow up, inpatient treatment should be considered. If a patient's symptoms are not improving after 48–72 h of outpatient treatment, inpatient management should be considered for intravenous antibiotics and further evaluation for alternative diagnoses.

10.2 Inpatient Management

10.2.1 Criteria for Inpatient Management

The following criteria should be used for inpatient management with intravenous antibiotics:

1. Surgical emergencies (i.e., ovarian torsion or appendicitis) cannot be excluded.
2. Failed outpatient management.
3. Unable to follow or tolerate the outpatient oral antibiotic regimen (consider for vulnerable populations such as adolescents or drug users).
4. Severe infection (severe pain, nausea, vomiting, high fevers >38.3 °C, sepsis).
5. Tubo-ovarian abscess.
6. Pregnancy.

10.3 Inpatient Course of Treatment

Recommended parenteral antibiotic regimens are shown in Table 2. Intravenous antibiotics should

Table 1 Oral/intramuscular treatment (CDC 2015b)

OR	Ceftriaxone 250 mg IM in a single dose
	Cefoxitin 2 g IM in a single dose and probenecid 1 g orally in a single dose
	Other parenteral third-generation cephalosporin (ceftizoxime or cefotaxime)
PLUS	Doxycycline 100 mg orally every 12 h for 14 days
+/−	Metronidazole 500 mg orally every 12 h for 14 days **(given for BV)**

IM intramuscular, *BV* bacterial vaginosis (diagnosed by saline microscopy)
Alternative to doxycycline: azithromycin 1 g orally weekly for 2 weeks can be given instead of doxycycline

be given for at least 24 h. After 24–48 h with improvement in clinical symptoms (afebrile and improved pain), patients may be transitioned to oral antibiotic regimen. Patients should be discharged with oral antibiotics to complete 14-day antibiotic course of doxycycline. Patients should be treated with metronidazole if also diagnosed with bacterial vaginosis. Patients with diagnosis of TOA should also be given metronidazole 500 mg orally twice daily or clindamycin 450 mg orally four times daily for 14 days to ensure effective anaerobic coverage.

10.4 Drainage of Tubo-ovarian Abscess

Drainage of tubo-ovarian abscess may be considered in a patient who does not respond to intravenous antibiotics and may be necessary in abscesses larger than 8 cm. TOAs are usually drained transvaginally with ultrasound guidance. Occasionally a short-term indwelling catheter remains in place for continued drainage.

11 Surgical Intervention

Surgery is usually not indicated in the diagnosis or treatment of acute infection. Surgery may be indicated to rule out other surgical conditions that could not be excluded clinically (i.e., ovarian torsion). In cases not improved by conservative measures including antibiotics with or without drainage of abscess, or in cases of TOA rupture, surgery by laparotomy may be indicated to remove purulent material and necrotic tissue. Surgery may also be indicated in postmenopausal women with TOA when malignancy cannot be excluded, though this is usually deferred until after completion of treatment for acute infection.

11.1 Intraoperative Findings

Laparoscopy can confirm acute PID if salpingitis or pyosalpinx is seen, but is not sensitive in detecting PID in a patient with only endometritis and mild intraluminal tubal disease.

Salpingitis may be identified by tubal serosal hyperemia, tubal wall edema, or purulent discharge from the fimbria of fallopian tubes or collection in the cul-de-sac. In patients with perihepatic inflammation (*Fitz-Hugh-Curtis syndrome)*, the classic intraoperative findings are *violin string adhesions* between the diaphragm and liver capsule that may be seen during acute PID or may suggest past infection.

12 Other Management Considerations

12.1 Patient Counseling and STI Testing/Reporting

Patients should be counseled about PID as a sexually transmitted infection. The patient should be offered testing for other STIs including HIV, syphilis, and hepatitis B. PID, *N. gonorrhoeae*, and *C. trachomatis* should be reported to the local public health department as a sexually transmitted infection. If the patient had positive testing for *N. gonorrhoeae* or *C. trachomatis*, she should be retested in 3–6 months. Repeat testing should not be performed prior to 6 weeks as results can be difficult to interpret. Sexual partners within the last 60 days, or the most recent sexual partner, should

Table 2 Parenteral treatment (CDC 2015b)

Regimen A	
OR	Cefotetan 2 g IV every 12 h
	Cefoxitin 2 g IV every 6 h
PLUS	Doxycycline 100 mg orally or IV every 12 h[a]
+/−	Metronidazole 500 mg orally every 12 h for 14 days (**given for BV**)
Regimen B (if severe B-lactam allergy)	
	Clindamycin 900 mg IV every 8 h
PLUS	Gentamycin: 2 mg/kg IV or IM loading dose followed by 1.5 mg/kg IV or IM every 8 h (single daily dosing may be given 3–5 mg/kg/day)
ORAL	Transition to oral clindamycin 450 mg orally every 6 h or doxycycline 100 mg orally every 12 h for 14 days
+/−	Metronidazole 500 mg orally every 12 h for 14 days (**given for BV**)
Alternatives	
	Ampicillin/sulbactam 3 g IV every 6 h
PLUS	Doxycycline 100 mg orally or IV every 12 h[a]

IV intravenous, *IM* intramuscular, *BV* bacterial vaginosis (diagnosed by saline microscopy)
[a]If a patient is able to tolerate oral doxycycline, it should be given orally. Intravenous doxycycline is associated with irritation and phlebitis. Oral and IV doxycycline have similar bioavailability

also seek evaluation and treatment. Patients should abstain from sexual intercourse while undergoing treatment until symptoms resolve and partners have been evaluated. Adherence and completion of antibiotics should be emphasized. The patient should be counseled on the use of condoms or other barrier contraception to prevent future sexually transmitted infection and should be offered additional birth control options.

12.2 Intrauterine Device (IUD) in Place

If an IUD is in place at the time of diagnosis of PID, the IUD may remain in place. It does not need to be removed. If the patient does not demonstrate clinical improvement after 48–72 h of appropriate antibiotic treatment, removal of the IUD may be considered (CDC 2015b).

12.3 Follow-Up

For outpatient treatment of PID, patients should be seen within 48–72 h for repeat pelvic exam. In all patients, strict return precautions should be given for worsening symptoms. For TOA, repeat pelvic ultrasound in 6 weeks to confirm resolution. A persistent adnexal mass, particularity in a postmenopausal woman, should prompt further evaluation for malignancy.

Fig. 6 Long-term complications

- Recurrent PID
- Hydrosalpinx
- Pelvic adhesions
- Chronic pelvic pain
- Infertility
- Ectopic pregnancy

13 Long-Term Complications

Prompt diagnosis and treatment are important to reduce the risk of long-term sequelae (Peipert and Madden 2015) (Fig. 6). Tubal inflammation damages both the secretory and ciliated endothelial cells within the tubal lumen, flattens mucosal folds, and also causes distortion of the fimbria leading to tubal clubbing, blockage, and adhesions. Hydrosalpinx or enlarged fluid-filled tubes may form secondary to blockage. Tubal damage and blockage may lead to infertility, ectopic pregnancy, and chronic pelvic pain. Patients are also at risk for recurrent PID.

Pain may develop due to hydrosalpinx or pelvic adhesions and may affect up to one third of women after PID. In a cohort that followed 100,000 young women with PID between the ages of 20 and 24 years, there were 18,600 cases

of chronic pelvic pain, 16,800 cases of infertility, and 8,550 ectopic pregnancies (Yeh et al. 2003). Studies also indicate that the rates of ectopic pregnancy and infertility increase with the number of episodes and severity of disease (Wiesenfeld et al. 2012). Thus, early recognition, prompt treatment, and prevention of recurrence are necessary to minimize long-term complications.

14 Conclusion

Pelvic inflammatory disease (PID) is an infection of the upper genital tract in females and is commonly encountered by healthcare providers in a variety of care settings: including obstetrics and gynecology, primary care, and emergency medicine/urgent care. The signs and symptoms of PID can be vague, and the diagnosis is made clinically. Given the significant long-term complications of delayed treatment or untreated PID, a low threshold for diagnosis and treatment is recommended. Healthcare providers may reference treatment guidelines developed by the CDC for both inpatient and outpatient management of PID and antibiotic regimens.

15 Cross-References

- Anatomy of the Female Genital System
- Management of Acute Pelvic Pain: Torsion, Rupture of Ovarian Mass
- Sexually Transmitted Diseases: Diagnosis and Work-Up (GC, Chlamydia, Herpes, HPV)

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Diagnosis and Treatment of Urinary Tract Infections

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Contents

Abstract

Urinary tract infections (UTI) are common among women of all ages and can vary in severity from uncomplicated, acute cystitis to pyelonephritis leading to urosepsis. There are various etiologies and risk factors for developing these infections across different population groups. Diagnosis is generally made based on the clinical presentation in conjunction with the presence of bacteriuria on urinalysis or urine culture. Depending on the classification of the UTI, management and treatment will vary. Preventive measures can also be undertaken to address risk factors. Most infections can be treated successfully and patients can expect to make a full recovery.

Keywords

Urinary tract infection • Cystitis • Pyelonephritis • Asymptomatic bacteriuria

1 Introduction

Urinary tract infections (UTIs) are common reason for women to seek gynecologic care. UTI can be caused by viruses or fungi like *Candida*, but the huge majority are bacterial in nature. In fact, UTI is one of the most common bacterial infections encountered in the ambulatory setting in the United States; 11% of US women report at least one physician-diagnosed UTI each year. According to the Centers for Disease Control

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and Prevention (CDC), more than six million women visited a medical provider for UTI in 2007; approximately 20% of those visits are to an emergency department. This pattern contributes to the large cost burden associated with UTI, with some studies estimating these infections cost upward of $1 billion annually.

UTIs in young, otherwise, healthy women who are not pregnant are generally considered to be uncomplicated. They can be treated with empirical antibiotics (discussed below), usually on an outpatient basis. A UTI is considered complicated if a structural or functional abnormality of the genitourinary tract is present. Simple UTI in pregnant women is not considered complicated. This distinction is important, because complicated UTI may need different empiric antibiotics and is more likely to require inpatient treatment.

UTI is widely regarded as a benign disease among medical practitioners because of the relatively innocuous natural history and because treatment of the majority of women with antibiotics is generally successful. However, patient perception of this health complaint is not always so benign. For example, when compared to women without UTI, women suffering from UTI rate their quality of life significantly lower with regard to general health perception, physical functioning, emotional health and well-being, vitality, pain, and social functioning. Lifestyle and behavior modifications may be suggested to prevent recurrent infection, and while effective, these can be difficult to initiate and maintain. An adept understanding of this prevalent condition is essential in gynecology and other primary care fields, with attention paid to both the physical and psychosocial sequelae.

Table 1 Risk factors for urinary tract infection

Premenopausal	Postmenopausal
History of UTI	History of UTI
Frequent or recent sexual activity	Vaginal atrophy
Diaphragm use	Incomplete bladder emptying
Use of spermicide	Poor perineal hygiene
Increasing parity	Pelvic organ prolapse
Diabetes mellitus	Type I diabetes mellitus
Obesity	
Sickle cell trait	
Anatomic abnormalities of the urinary tract	
Urinary tract calculi	
Requirement for bladder catheterization	

2 Definitions (Table 1)

- Asymptomatic bacteriuria

  Traditionally, 100,000 colony-forming units (cfu)/mL are considered significant bacteriuria. This definition is highly specific but only 50% sensitive. Some sources advocate lowering that cutoff to 1,000–10,000 cfu/mL in order to improve sensitivity of diagnosis. As the name implies, these women will have no symptoms of UTI regardless of the numerical definition of the term.

- Acute cystitis

  Acute cystitis is an infection of the lower urinary tract, namely, the bladder. Associated symptoms are produced by a local inflammatory response to bacterial infection: dysuria, hematuria, urinary frequency and urgency, and occasionally suprapubic pain. The natural history of acute cystitis is resolution in approximately 50% of cases, even without antibiotic treatment.

  Interstitial cystitis is a distinct entity in the spectrum of chronic pelvic pain not to be confused with acute cystitis discussed in the context of UTI. It is defined generally as pain/pressure/discomfort perceived to be associated with the urinary bladder for more than 6 weeks duration. There is no detectable infection or identifiable cause (i.e., urine cultures will be negative).

- Acute pyelonephritis

  Pyelonephritis implies infection that has ascended to affect the renal parenchyma, renal pelvis, and calices. Associated symptoms reflect an infection that produces a more systemic inflammatory response than what is seen in acute cystitis: fever and chills, flank pain,

and leukocytosis in addition to the urinary symptoms associated with lower UTI.

Chronic pyelonephritis results from persistent infection of the renal parenchyma causing scarring and fibrosis. End-stage renal disease can result.

- Persistent or relapse refers to UTI with the same organism after adequate treatment.
- Reinfection or recurrent refers either to a UTI with a different organism than that which was originally isolated or reinfection with the same isolate after an intervening negative culture. Either state might prompt a change in antibiotic therapy for that woman.
- Recurrent UTI.
  - Defined as $\geq$2 infections in 6 months or $\geq$3 infections in 1 year.
  - Most recurrences are thought to represent reinfection rather than relapse. Recurrence due to relapse warrants a more extensive urological workup, because a persistent nidus may be responsible requiring longer therapy or even surgery to eradicate it. This distinction is rarely clinically important in young healthy adult women (the most common UTI patient).

3 Epidemiology

Fifty percent of all adult women self-report having been diagnosed with UTI by that age of 32. The lifetime probability that a woman will suffer from a UTI is 60%. Prospective cohort studies estimate the incidence of acute cystitis between 0.5 and 0.7 cases per person-year among young sexually active women; incidence of culture-confirmed acute cystitis among postmenopausal women is 0.07 episodes per person-year (Hooton et al. 1996; Jackson et al. 2004). Generally, the risk for UTI increases with age.

UTI in the pediatric population is often due to congenital abnormalities of the urinary tract. Vesicoureteral reflux and constipation are also common causes of UTI in infants and children. Infrequent diaper changing promotes bacterial colonization. In young boys, posterior urethral valves are a well-described congenital variant that predisposes to UTI via obstructed urine flow from ureters to bladder. Circumcision has been shown to significantly reduce rates of UTI in male babies in the first year of life: one study showed a rate of 2.15% in uncircumcised boys versus 0.22% in circumcised boys (Schoen et al. 2000). Gram-negative rods (*E. coli*) are the most common causative agents, but *Candida* species (which cause tinea cruris, known colloquially as diaper rash) are important pathogens in this age group.

- Two notable spikes in incidence above baseline occur at age 18–30 years and in the postmenopausal stage. The former is attributable in increased coitus and pregnancy; the latter is associated with atrophic changes in the vagina, a shift in vaginal flora composition, bladder or uterine prolapse, and increased comorbid illnesses like diabetes. Acute pyelonephritis is less common than acute cystitis, with annual incidence estimated to be 12–13 cases per 10,000 women.

Recurrent uncomplicated UTIs are common in young healthy women: in one study, 27% of college women experienced a recurrence within 6 months of their first UTI, with an additional 2.7% experiencing a second recurrence in that time period (Foxman 1990). The chances of a recurrence increase with each subsequent recurrent infection. Recurrences are usually acute cystitis due to *E. coli*; recurrent pyelonephritis is rare in healthy patients and no prevalence data is available.

Pregnant women are an important subset when considering UTI. While the incidence of bacteriuria is approximately the same in pregnant and nonpregnant women, pregnant women are more likely to have recurrent bacteriuria. Asymptomatic bacteriuria occurs in up to 7% of pregnant women and is most common in the first trimester, with 75% of cases occurring during this time. More than one-third of pregnant women with bacteria in the urine will develop UTI (cystitis or pyelonephritis); however, this risk is reduced by

70–80% if the bacteriuria is treated with antimicrobials. Asymptomatic bacteriuria in pregnancy is associated with preterm birth and consequently low birth weight infants. Therefore, it is recommended to treat this condition in pregnant women in order to improve pregnancy outcomes and reduce the risk of pyelonephritis (more on this below). Acute cystitis occurs in 1–2% of pregnant women; pyelonephritis has an incidence of 0.5–2% in pregnancy and usually occurs in the second and third trimesters when the gravid uterus is most likely to occlude the ureters and predispose to stasis.

Between 30% and 50% of renal transplant patients suffer from UTI. However, many of these infections are "silent" or asymptomatic because the immunosuppressive drug regimens required after transplant suppress the body's inflammatory response to urinary tract bacterial colonization.

4 Pathogenesis

The normal urinary tract is sterile. Several natural defense mechanisms exist to prevent disruption of this sterile environment. The normal vaginal flora is composed primarily of lactobacilli, coagulase-negative staph, corynebacterium, and streptococci (group B streptococci). This population maintains a homeostatic biosphere and prevents overgrowth of foreign bacterial pathogens. Lactobacilli in particular contribute to maintenance of a normal vaginal pH ~3.5–4.5. Reduced estrogen levels or use of antibiotics can decrease the density of lactobacillus population. Cervical production of IgA also prevents vaginal colonization with nonnative bacterial species. Normal urine has a high osmolality due to high urea concentrations. Urea is naturally antimicrobial and protects against infection. Organic acids like ammonium confer urine with a low pH, which is also protective.

The urothelium is normally shed every few days, so adhered bacteria will also slough off and be excreted via the urine. Additionally, bladder epithelium expresses Toll-like receptors (TLRs). Surface-expressed TLRs, like those found in the bladder, respond primarily to cell wall components of bacteria. Upon recognition of a pathogen, TLRs trigger phagocytic and maturation signals to recruit immune cells, as well as providing co-stimulatory signals in CD80- and CD86- positive B cells. Host defenses in the kidney are primarily composed of IgG and IgA production.

UTI occurs when one or more of these normal defenses are disrupted. Generally, three main mechanisms are responsible for UTI:

Colonization with ascending spread

- This is the most common mechanism.
- Pathogens that cause urinary tract infection originate in either the bowel or the vagina (via direct inoculation, e.g., during sexual activity). The mucosa of the urethral meatus is colonized, and the bacteria ascend into the urethra and bladder from this point.
- The female urethra is short compared to the male urethra and in close proximity to both the vagina and the anus.
- Cystitis represents bacterial invasion of bladder mucosa and consequential local inflammatory response.

E. coli is the most commonly implicated bacterial species in this type of UTI. *Staphylococcus saprophyticus* accounts for up to 15% of UTI in young sexually active women. Hematogenous spread

- This is a rare cause of UTI, usually seen in immunocompromised patients and neonates.
- Incompletely treated pyelonephritis, especially emphysematous pyelonephritis, can cause a relapsing UTI via hematogenous spread.
- Hematogenous UTIs are more likely to be due to *Staphylococcus* species (especially *S. aureus*). Mycobacterium tuberculosis and *Candida* species can also cause UTI via hematogenous spread.

Periurogenital spread

- An infection involving another organ in the genitourinary or gastrointestinal systems can

spread to affect the bladder, causing acute cystitis.
- *E. coli* is still the most common bacterial species to cause UTI via this mechanism, but pathogens which cause vaginitis and enteritis are also implicated.
- Circumstances that delineate asymptomatic bacteriuria from actual UTI are not clear. Rates of UTI do not differ between groups with asymptomatic bacteriuria treated with antibiotics versus no treatment.

5 Risk Factors (Table 2)

Risk factors for UTI can be categorized into three main subsections:

1. Factors which reduce urine flow (promote stasis)
   - Outflow obstruction can occur from urinary tract calculi. Inadequate fluid intake both predisposes to urinary tract calculi and contributes to low urinary flow. Urethral strictures can occur following urethritis or traumatic catheterization. Reduced activity of the detrusor muscle can occur following spinal cord injury to the sacral nerve roots at S2–S4, interrupting parasympathetic stimulation that normally contracts the bladder in the voiding phase. Diabetes mellitus can cause a similar clinical picture as glycated end products damage nerves and blood vessels resulting in cystic neuropathy. Most cases of UTI in diabetics are in the upper genitourinary tract because of reflux of urine from a neurogenic bladder into the kidney. Glucosuria may also contribute to virulence of UTI pathogens in diabetics. Use of anticholinergic medications can decrease detrusor activity and cause urinary retention.
   - Sickle cell anemia can be complicated by papillary necrosis as sickled red blood cells occlude the microvasculature to the renal pelvis. Necrosed papilla can break off of the calices and fall into the proximal ureter, causing obstruction.
   - Pelvic organ prolapse becomes more common with age, especially if a woman has been pregnant and has had vaginal deliveries. Uterine or bladder prolapse can obstruct normal urine flow and cause urine retention.
   - In children and adolescents, congenital abnormalities of the urinary tract can cause abnormal urine flow and predispose to UTI. In young girls, the most common cause is vesicoureteral reflux from incompetent valves at the ureteral orifice into the bladder.
   - Chronic constipation can obstruct urine flow as the rectum dilates with stool and impinges on surrounding structures.
   - Increased progesterone levels in pregnancy cause decreased ureteral peristalsis and contraction pressure. The gravid uterus lateralizes the ureter and increases tortuosity and in some cases contributes to ureteral compression. This combination of factors predisposes to urinary stasis.
2. Factors which promote colonization
   - Increased sexual activity (especially involving vaginal penetration) contributes to UTI as it provides more opportunities for inoculation of foreign bacteria into the urethrovaginal area. The female urethra is small and in close proximity to the vaginal

Table 2 Key definitions

Asymptomatic bacteriuria	Significant bacteriuria in a woman with no symptoms
Acute cystitis	Infection limited to the lower urinary tract (bladder) associated with dysuria, frequency and urgency of urination, and suprapubic pain
Acute pyelonephritis	Infection of the renal parenchyma and pelvicaliceal system associated with fever and flank pain
Reinfection	Recurrent UTI caused by the same organism after adequate treatment and an intervening negative culture OR
	A recurrent UTI caused by a second, different isolate
Relapse	Recurrent UTI with the same organism after adequate therapy
Recurrent	Two or more infections in 6 months or three or more infections in 1 year, usually representing reinfection rather than relapse

introitus, so bacteria can access the urethra from the vagina with relative ease.

- Increased sexual activity, especially with multiple partners, is a risk factor for sexually transmitted infections. If those infections are treated with antibiotics, the normal vaginal biosphere is disrupted. Changes in flora patterns and vaginal pH allow nonnative bacteria to grow unchecked and cause infection.

  Use of spermicide and vaginal lubricants facilitates bacterial binding to vaginal and urethral mucosa, allowing for ascent into the bladder and beyond.

3. Factors which facilitate bacterial ascent
   - The most important culprit in this category is the bladder catheter. Whether a patient lives with an indwelling or undergoes intermittent catheterization, this device provides a variable highway for bacteria directly into the bladder. Patients with indwelling catheters are frequently immobile and/or elderly and have difficulty with urogenital hygiene, making it more likely that uropathogenic organisms will be in the region.
   - Postmenopausal women are particularly predisposed to UTI because of changes related to decreased levels of circulating estrogens. Atrophic vaginal mucosa is less able to heal and fight infection, and the lactobacilli bacteria that maintain normal vaginal homeostasis premenopause are a smaller component of the genital flora. Estrogen deficiency also reduces the urethral mucus that serves as a barrier to bacteria getting into the bladder. Postmenopausal risk factors for recurrent infections include urinary incontinence and the presence of a cystocele. ABO blood group antigen secretor status is also important in the context of postmenopausal women and recurrent UTI. Most people (80%) secrete these antigens in their saliva, gastrointestinal mucous, tears, and other fluids. However, those who do not secrete these antigens have a more robust inflammatory response to urinary tract infection and are more likely to have recurrent infections. Of note, nonsecretor status is also associated with uncomplicated pyelonephritis in premenopausal women.
   - Diabetes, obesity, and sickle cell anemia are all associated with micro- and macrovascular disease. Damage to blood vessels (via glycated end products in diabetes mellitus, atherosclerotic changes in obesity, and occlusion in sickle cell anemia) impedes blood flow to the pelvic floor, preventing optimal immune response to bacterial colonization.
   - Women who suffer from recurrent acute cystitis generally have normal urinary tracts. Loss of lactobacillus is one of the most consistently identified risk factors for recurrent infection. Genetic determinants have also been identified, such as an increased propensity for uropathogens to adhere to the uroepithelium in women with recurrent UTI versus women without recurrent infection. Maternal history of UTI is also associated with recurrent infections, supporting a genetic component. Behavioral risk factors also play a large role, including spermicide use and/or new sexual partner(s) in the preceding year.

6 Microbiology

- The most common cause of uncomplicated acute cystitis and pyelonephritis in women is *Escherichia coli*, accounting for 95% of all cases of UTI in women.
- *Staphylococcus saprophyticus* is a coagulase-negative species that is a common causative agent in sexually active women of childbearing age. Resistance to novobiocin differentiates *S. saprophyticus* from other coagulase-negative staphylococci.
- *Enterobacteriaceae* species make up the remaining cases. *Proteus mirabilis* and *Klebsiella pneumoniae* are common culprits, especially in recurrent, complicated, and catheter-associated UTI.
- Uropathogenic or extraintestinal pathogenic *E. coli* (ExPEC) has virulence and fitness

factors that enhance the bacteria's ability to cause symptomatic infection. These factors include flagella, adhesins, toxins, polysaccharide coatings, and others. These diverse attributes allow the bacteria to avoid host defenses and adhere to uroepithelium. Invasion of or damage to host cells by the bacteria stimulates an inflammatory response, producing the constellation of symptoms characteristic of UTI.

- Specifically, bacterial expression of a specific adhesin, type I fimbriae, has been identified as a reproducible and important virulence factor in acute cystitis. Type I fimbriae facilitate tissue attack and adhesion to bladder mucosa.
- *E. coli* is still the most common causative agent in complicated UTI in women, although strains causing complicated infections tend to have atypical virulence characteristics. Urease-producing organisms like *Proteus mirabilis*, *Providencia stuartii*, and *Morganella morganii* are common among patients with indwelling urological devices like urinary catheters. Proteus infections are notorious for causing struvite renal calculi, which protect the bacteria from antimicrobial treatment and result in infection that is difficult to eradicate. Overall, complicated UTI in catheterized patients is most commonly polymicrobial. *Pseudomonas aeruginosa* infection (associated with diabetes mellitus) can also become persistent, as this organism has intrinsic resistance mechanisms that protect it from host defenses.
- Patient education on proper clean-catch urine sample acquisition is critical. Contamination with normal vaginal or skin flora clouds the clinical picture because (though rare) some of these isolates can cause infection in the case of recurrent or complicated UTI. Isolation of lactobacilli, enterococci, group B streptococci, and coagulase-negative staphylococci other than *S. saprophyticus* is likely contaminated. Repeated urine sampling is inconvenient for the patient and wastes healthcare system resources.

7 Resistance Trends

- It is exceptionally important that a practitioner treating UTI be familiar with local patterns of antibiotic resistance. A working knowledge of this topic is a moving target, because resistance patterns vary widely based on geographical location and can change with relative rapidity. The Center for Disease Dynamics, Economics, and Policy has created an antibiotic resistance pattern map, with data for many countries including the United States. It can be found online at http://www.cddep.org/projects/resistance-map.
- These trends are essential especially with regard to *E. coli* resistance. Several studies have demonstrated more than 20% of *E. coli* strains causing UTI are resistant to ampicillin. Trimethoprim (a component of Bactrim, an important empiric antibiotic) also has high resistance rates, some studies suggesting close to 20% in certain geographic regions.
- Fluoroquinolones still have low resistance rates in most of the United States, and current antibiotic stewardship recommendations attempt to protect that drug class against inappropriate use. Ciprofloxacin is a fluoroquinolone commonly prescribed for UTI, but bacterial (*E. coli*) resistance rates to this drug unfortunately increased from 3% to 17% from 2000 to 2010.
- Resistance to first- and second-generation cephalosporins and amoxicillin-clavulanic acid is generally $<10\%$. Nitrofurantoin also has low resistance rates. This suggests that any of these drugs may be appropriate empiric therapy in the setting of uncomplicated UTI. However, rates of infection with extended-spectrum beta-lactamases are increasing, a worrisome statistic with regard to empiric use of cephalosporins and amoxicillin-clavulanic acid.
- Trimethoprim-sulfamethoxazole (TMP-SMX) is currently the recommended empiric drug of choice and has the most data available to guide

clinical use. Local resistance prevalence >20% is suggested as the cutoff at which TMP-SMX should not be used. At this threshold, mathematical modeling and clinical and in vitro data suggest risks outweigh the benefits of TMP-SMX use.
- Multidrug resistant strains of bacteria are particularly prevalent among elderly and catheterized patients. This may be because these populations of patients tend to get more antibiotics (for UTI and otherwise), and drug-resistant organisms are selected out as other pathogens are eradicated by the drug therapy.

8 Complications of UTI

- In the vast majority of uncomplicated UTI, prognosis is excellent. The infection may resolve even without antibiotic therapy in some cases. Most morbidity associated with uncomplicated UTI emerges when the infections are recurrent. The disease is very uncomfortable, painful, and disturbing to women who suffer from it. The cost and loss of productivity associated with physician visits and therapy are a burden. Multiple cases of acute pyelonephritis can cause permanent damage to the renal parenchyma similar to the morbidity associated with chronic pyelonephritis. Glomerular filtration rates can be compromised as a result.
- Complicated UTIs are more frequently associated with serious morbidity. Some of the most common complications are suppurative in nature: paraurethral, renal, or perirenal abscesses have been described. Infection can spread to the bones and joints causing osteomyelitis and/or septic arthritis. Endocarditis can also be caused by metastatic infection. At the extremes of age or in the case of immunocompromised, acute urinary tract infection can result in septic shock and even death. Complications are more likely in diabetics, chronic catheter use, and in cases of urinary obstruction.

9 Prevention

- Especially in the context of recurrent disease, many behavioral changes and alternative pharmaceutical therapies have been proposed to prevent UTI. It is important to bear in mind that few of these have been adequately tested via research study, but it is reasonable to advocate for them in order to reduce antibiotic use. Most of them carry a very low risk for harm and may work for some patients via mechanisms not yet identified.
- Women should avoid contraception with spermicide, especially in conjunction with a diaphragm or cervical cap.
- Postcoital voiding has been suggested as a preventative measure, citing the theoretical mechanism that urine flow would "wash out" bacteria at the urethral meatus and prevent ascension. To facilitate increased voiding in general, liberal fluid intake to increase micturition is also advocated.
- Cranberry juice.
  - Cranberry juice is one of the most well-known methods to prevent UTI among the laywoman. The proposed mechanism is inhibition of bacterial adhesion. Fructose may interfere with type 1 fimbriated *E. coli* adhesion specifically (Zafriri et al. 1989). Proanthocyanidins, another component of cranberry juice, prevent adherence of P-fimbriated *E. coli* (Howell et al. 1998).
  - Some providers have strong biases (positive or negative) about the effectiveness of cranberry juice. Nevertheless, controlled trials have yielded equivocal data regarding the prevention of uncomplicated cystitis. Attempts to meta-analyze the abundance of research on this topic are limited by heterogeneity of the studies in terms of delivery method of the cranberry extract (tablets vs. liquid concentrate, etc.), lack of blinding, lack of placebo group, and lack of a uniform operational definition of UTI.
  - A trial of cranberry extract is probably safe for most women who want to try it. Because of the acidity of the juice, women may

experience gastric acid reflux and other gastrointestinal complaints. This is especially true in patients using cranberry juice for prolonged periods of time.

- Probiotics.
  - Lactobacillus probiotics have been proposed as a prophylactic measure for recurrent UTI sufferers. Suggested mechanisms include maintenance of a pH <4.5, anti-inflammatory effects of epithelial cells, production of hydrogen peroxide (microbicidal to *E. coli*), and physical blockade of attachment sites. Oral administration has not been shown to achieve detectable levels of colonization when testing for the specific strain of lactobacillus is done using polymerase chain reaction amplification (Barrons and Tassone 2008). Furthermore, meta-analysis of the data reveals that the majority of studies (7:1) do not show a therapeutic effect for oral lactobacillus. Many women also discontinued the oral form due to side effects, mostly related to gastrointestinal upset (Beerepoot et al. 2012). Vaginal suppositories show more promise. This form was much better tolerated than the oral administration and achieved higher levels of vaginal colonization compared to oral administration. Most importantly, vaginal delivery of lactobacillus was shown in a small study to decrease rates of recurrent UTI: 15% versus 27% in the placebo group Stapleton et al. 2011).
- Topical estrogen.
  - Topical estrogen contributes to normalization of vaginal flora and therefore reduces the risk of UTI in postmenopausal women. One study reports use of intravaginal estriol cream over the course of 8 months reduced the incidence of UTI fivefold (Raz and Stamm 1993).
  - Topical estrogen has the added benefits of reducing atrophic vaginal changes and vaginal dryness and dyspareunia in this population.
- Vaccinations and vaginal suppositories containing heat-killed uropathogenic bacteria have been tested with only marginal success. Protective effects seem to decrease rapidly, over the course of several weeks. OM-89 is an immunostimulant made from the extract of several strains of heat-killed uropathogenic *E. coli*. When given orally, they do appear to reduce incidence of UTI. It is currently unavailable in the United States, but is commercially available in Europe.
- Methenamine salts are converted to formaldehyde in acidic urine, conferring an antimicrobial activity that could theoretically prevent UTI at the level of the bladder. However, they are not recommended for routine use in young women. While some reports do show a small benefit in a very specific subset of patients (women with renal tract abnormalities who underwent gynecologic surgery), considerable methodological flaws have been identified in those studies. Anecdotal evidence exists for women with recurrent infections with multidrug-resistant organisms; the drug appears to be safe and well tolerated, so further investigation is warranted into its effectiveness as an antimicrobial alternative.
- Antimicrobial prophylaxis is discussed in the treatment section of this chapter.

10 Diagnosis and Management

Urinary tract infections in nonpregnant women are diagnosed clinically and confirmed by the presence of bacteriuria on urinalysis and urine culture. If a woman presents with symptoms consistent with a UTI, but has no history of laboratory confirmed UTI, a urinalysis or dipstick is typically performed to confirm the diagnosis. However, if the patient has a history of frequent recurrences, prior confirmation with laboratory testing, and is symptomatic, she can be treated empirically without performing a urinalysis. A urine culture is only indicated when there is no clinical improvement after 48 h of treatment, if recurrent, and in all cases of pyelonephritis.

Pyuria and bacteriuria can be assessed using commercially available urine dipsticks. Leukocyte esterase and nitrites are commonly tested for, and their presence has a sensitivity of 75%

and a specificity of 82% in predicting UTI. Leukocyte esterase is an enzyme released by leukocytes and is indicative of pyuria. Some bacteria, such as the *Enterobacteriaceae* family, reduce urinary nitrates to nitrite so the presence of nitrites indicates bacteriuria. However, a positive urine dipstick test provides little useful information given symptoms strongly suggestive of UTI.

- Acute Cystitis

  Acute, uncomplicated cystitis is typically diagnosed clinically. There is a >90% probability that a woman who presents with at least two of the following symptoms, dysuria, frequency, or urgency in the absence of vaginal discharge, has acute cystitis. Moreover, studies have shown that in women with symptoms of acute cystitis, obtaining urinalysis or urine culture is not associated with improvements in symptom scores or time to reconsultation compared to immediate empirical therapy.

  In addition to office visits, women with suspected acute, uncomplicated cystitis may also be managed via telephone or with patient-initiated therapy. Telephone management involves screening patients for the symptoms of acute cystitis and for risk factors for complicated UTI, pyelonephritis, and sexually transmitted infections. Women who meet criteria for telephone management (Table 3) can thus be managed by avoiding an office visit and having a prescription called into the pharmacy. Patient-initiated therapy may be appropriate in women with a history of UTI who can identify symptoms, have an existing patient-clinician relationship, and are educated on when to seek additional care (new symptoms of vaginal discharge, back pain, fever, missed menstrual period, new sex partner, etc.). In this approach, patients are prescribed antibiotics to keep at home or are given a prescription to fill when needed. Studies have shown that among these patients, the rate of correct diagnosis was more than 90%.

  There are several antibiotic treatment options for uncomplicated, acute cystitis. First-line agents include trimethoprim-sulfamethoxazole 160/800 mg twice daily for 3 days if resistance prevalence is <20%, if there has been no use in the past 6 months, or if no recent travel to an endemic area of resistance, nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for 5–7 days or a 3 g single dose of fosfomycin trometamol. Although fluoroquinolones are highly efficacious for treating uncomplicated cystitis, they are second-line agents due to increasing resistance rates and are reserved for use in more invasive infections. Generally, beta-lactam agents, such as amoxicillin-clavulanate and cefpodoxime proxetil, are not used as they have been shown to have inferior efficacy compared to other antimicrobial agents in treating UTIs.

  There have been several studies on alternative treatment options for acute cystitis in non-pregnant patients. However, evidence has shown that these methods, including placebo treatment, delayed antibiotic therapy, and ibuprofen therapy, are not helpful and may actually be harmful.

- Acute Pyelonephritis

  Acute pyelonephritis is diagnosed clinically and with a urine culture. Patients presenting with acute pyelonephritis will typically have fever, chills, flank pain, costovertebral angle tenderness, and nausea or vomiting. They may or may not have symptoms of cystitis (dysuria, frequency, urgency). A urine culture must be done to confirm bacteriuria and identify the infecting uropathogen to tailor the antimicrobial treatment. Traditionally, acute

Table 3 Criteria for telephone management of acute cystitis

Adult women with acute onset (<7–10 days) + >1 of the following: dysuria, frequency, urgency, gross hematuria
No flank or abdominal pain
Afebrile (<100.5 °F)
Able to urinate in past 4 h
Can tolerate oral medications
Not pregnant
No comorbid conditions or voiding abnormalities
No history of sexually transmitted infections
No new sex partner
No vaginal symptoms
No recent UTI (past 4–6 weeks) or urological procedure

Table 4 Outpatient treatment of acute pyelonephritis

Oral ciprofloxacin 500 mg twice daily for 7 days[a]
Oral ciprofloxacin 1,000 mg extended release for 7 days[a]
Oral levofloxacin 750 mg for 5 days[a]
Oral trimethoprim-sulfamethoxazole 160/800 mg twice daily for 14 days[b]

[a]If >10% prevalence of fluoroquinolone resistance, recommended to have an initial IV dose of a long-acting parenteral antibiotic (1 g ceftriaxone or consolidated 24 h dose of an aminoglycoside)
[b]If susceptibility data unknown, recommended to have an initial IV dose of a long-acting parenteral antibiotic (1 g ceftriaxone or consolidated 24 h dose of an aminoglycoside)

pyelonephritis was treated in the inpatient setting; however, if the patient is hemodynamically stable without any complicating factors such as diabetes or pregnancy and can tolerate and be compliant with oral medications, they can be managed in the outpatient setting. After obtaining the urine culture, empiric antimicrobial treatment (Table 4) can be initiated and then tailored when the culture results and susceptibilities return.

Fluoroquinolones are first-line agents for empiric outpatient treatment, but other acceptable options include trimethoprim-sulfamethoxazole or a beta-lactam if susceptible. In the inpatient setting, intravenous broad-spectrum antibiotics, such as fluoroquinolones, aminoglycosides, extended-spectrum cephalosporins, extended-spectrum penicillins, or carbapenems, can be used. If the patient improves clinically and can tolerate oral medication, she can be transitioned from intravenous to oral antibiotics. If there is no clinical improvement in 48–72 h, the urine culture should be repeated with initiation of another empiric antimicrobial treatment. Follow-up urine cultures are not needed if there is resolution of symptoms.

- Pregnancy (Fig. 1)
  - Asymptomatic Bacteriuria

    Routine urine culture is performed at 12–16 weeks gestation to screen for asymptomatic bacteriuria during pregnancy as the risk for developing pyelonephritis is increased. It is generally recommended that women collect a clean-catch midstream urine sample, but it is still uncertain whether these methods reduce contamination. Routine catheterization for screening is not necessary. Asymptomatic bacteriuria is defined as >10^5 colony-forming units (cfu)/mL of the same bacterial strain on two consecutive voided urine samples or >100 cfu/mL of a single bacterial strain on one catheterized urine sample. However, clinically, only one voided urine sample is obtained, and diagnosis is made without a repeat culture if >10^5 cfu/mL are found.

    Management of asymptomatic bacteriuria during pregnancy consists of antimicrobial therapy, as well as with follow-up cultures to confirm eradication of the bacteriuria. Antimicrobial therapy is tailored to the urine culture results and susceptibilities with consideration taken to which antibiotics are safe to use during pregnancy. Although there is no optimal duration of therapy, a short course of antibiotics is typically preferred. One week after the completion of antibiotic therapy, a test of cure is performed, and monthly urine cultures are repeated until the end of the pregnancy due to the risk of persistent or recurrent bacteriuria.

    Persistent bacteriuria occurs when the first urine culture for the test of cure continues to have >10^5 cfu/mL of the same bacterial isolate. In these cases, the same antimicrobial is continued for a longer duration, or a different antibiotic is used in a standard regimen. If the bacteriuria persists after two or more courses of therapy, then a suppressive therapy for the duration of the pregnancy may be appropriate. If suppressive antimicrobial therapy is begun, monthly cultures are not necessary, but typically one later culture usually at the start of the third trimester is performed to ensure that the therapy is working. In the event that the follow-up culture while on suppressive therapy turns out positive, another course of antimicrobials based on

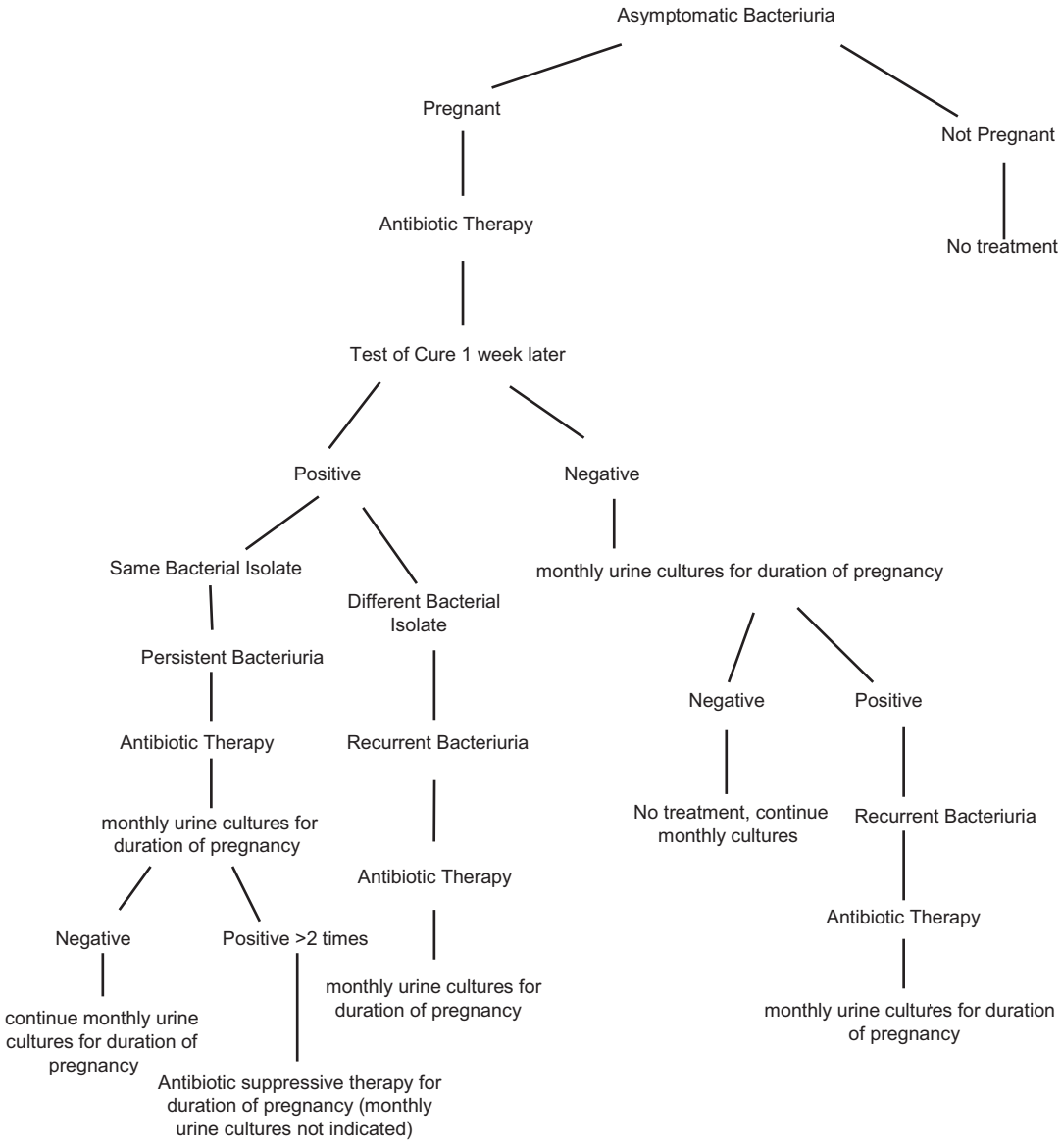

Fig. 1 Management of asymptomatic bacteriuria

susceptibility data should be administered and the suppressive regimen readjusted if needed.

Recurrent bacteriuria occurs when the test of cure comes back positive for a different bacterial isolate or when the test of cure comes back negative, but a subsequent culture is positive for either the same or a different species. Based on susceptibility data, another course of antimicrobials is then administered. Antibiotic prophylaxis is generally not indicated for recurrent asymptomatic bacteriuria.

– Acute Cystitis

When a pregnant woman complains of new-onset dysuria, a urinalysis and urine culture should be performed on suspicion of acute cystitis. However, it is important to note that urinary frequency and urgency can be normal physiologic findings of

pregnancy. If pyuria is found on urinalysis and symptoms are consistent with cystitis, empiric treatment with antibiotics can be given. Diagnosis is confirmed with bacterial growth on urine culture. There have been no studies defining the threshold for bacterial growth in pregnant women, but >10^3 cfu/mL with symptoms is typically indicative of cystitis. However, if the isolated bacteria is not a typical uropathogen, generally a higher bacterial count of >10^5 cfu/mL is needed for diagnosis. Empiric therapy is generally begun with either cefpodoxime, amoxicillin-clavulanate, fosfomycin, or nitrofurantoin (if during second or third trimester), and then treatment is tailored based on the results of the urine culture and susceptibilities. The optimal duration of treatment is uncertain, but antibiotics are generally given for 3–7 days, and a test of cure is performed 1 week after completion of therapy. Monthly urine cultures are also performed for the duration of the pregnancy due to risk of persistent or recurrent bacteriuria. If cystitis is recurrent, daily prophylaxis is appropriate with either 50–100 mg PO nitrofurantoin or 250–500 mg PO cephalexin at bedtime or postcoitally (if thought to be sexually related).

– Acute Pyelonephritis

Acute pyelonephritis is diagnosed based on the clinical picture and confirmed by bacteriuria on urinalysis and urine culture. Clinically, a patient will present with flank pain, nausea/vomiting, fever, and/or costovertebral angle tenderness. Symptoms of cystitis may or may not be present. Given the adverse outcomes associated with pyelonephritis in pregnancy such as preterm birth, anemia, sepsis, and respiratory distress, the threshold for evaluation of pyelonephritis is low. Imaging is not routinely performed; however, if needed, renal ultrasound is preferred.

Pregnant patients are generally treated for pyelonephritis in the inpatient setting with intravenous antibiotics until symptomatically improved with no fever for 24–48 h. Broad-spectrum beta-lactams are preferred for empiric therapy with tailoring done to the urine culture results and susceptibility data. Although, fluoroquinolones and aminoglycosides are used to treat non-pregnant women, they should be avoided in pregnancy if possible. Once the patient has been afebrile for 48 h,, therapy can be switched to oral antibiotics, and the patient can be discharged home to complete a total of 14 days of treatment. However, if fever and symptoms persist despite treatment, a repeat urine culture and renal ultrasound should be done to rule out renal abscess. Low-dose suppressive antimicrobial therapy is typically administered for the duration of the pregnancy to prevent recurrence of pyelonephritis. However, if suppressive therapy is not administered, monthly urine cultures should be done.

• Older Women >65 years

In older women, the diagnosis of UTI becomes more difficult as asymptomatic bacteriuria is common in the elderly, and older adults will often have genitourinary symptoms such as urgency, incontinence, and dysuria. If there is a clinical suspicion of UTI in women >65 years and they present with nonspecific symptoms and signs, management options include either oral or IV hydration, current medication modification (e.g., discontinuation of diuretic), or topical vaginal estrogen if the vaginal mucosa appears hypoestrogenic. If after 24–48 h of observation, there are changes in mental status or in the character of the urine, a urine dipstick should be performed. If the dipstick is positive, a urine culture should be obtained, but if it is negative, further evaluation for a UTI should be stopped, and other diagnoses should be considered. If the urine culture returns positive and the symptoms persist, a short course of antibiotics may be appropriate. However, if the symptoms resolve regardless of the culture results, no treatment is indicated. If the culture is negative with persistent symptoms, other etiologies must be evaluated. If there is a clinical suspicion of UTI and the woman presents with UTI-specific signs and

symptoms such as fever, new or worsening dysuria, new urinary incontinence, or costovertebral angle tenderness, then a urine sample must be sent for urinalysis and culture with subsequent treatment with empiric antibiotics. If the urinalysis or culture returns negative, antibiotics should be stopped, but if positive, they should be continued for 3–14 days depending on the severity of the infection. If the symptoms resolve with antibiotic treatment, a test of cure is not necessary after the completion of therapy.

11 Conclusion

- UTIs are a common complaint among women and have a spectrum of severity. They are typically diagnosed clinically and confirmed by the presence of bacteriuria. Asymptomatic bacteriuria is a benign condition and can be left untreated unless pregnant. Acute cystitis is generally uncomplicated and can be treated on an outpatient basis with a short course of antibiotics with management not always requiring an office visit. Pyelonephritis is the most severe of the UTIs and can be managed both in the inpatient and the outpatient setting. Generally speaking, UTIs have an excellent prognosis with most patients being successfully treated with antibiotics and making a full recovery.

12 Cross-References

- ▶ Current Recommendations in Gynecology: Preventive Health Care, Screening, Immunizations
- ▶ Management of Pelvic Pain in the Older Woman
- ▶ Sexually Transmitted Diseases: Diagnosis and Work-Up (GC, Chlamydia, Herpes HPV)

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Diagnosis and Management of Endometriosis

Angela S. Kelley and Molly B. Moravek

Contents

Abstract

Endometriosis is a chronic, benign gynecologic condition, affecting up to 10% of reproductive-age women. It is characterized by the abnormal presence of endometrial glands and stroma outside of the uterus. Clinically, endometriosis is associated with dysmenorrhea, pelvic pain, and/or infertility. The diagnosis of endometriosis can be suggested based on history and physical examination, but the gold standard for diagnosis is histologic confirmation from a surgical biopsy. The stages of endometriosis are determined based on the extent of disease intraoperatively. However, the stages of disease do not always correlate well with symptom severity. Treatments include pain management, hormonal suppression, and/or surgical intervention. Treatment decisions must be individualized to each patient, taking into consideration her symptoms and her plans for future fertility. Endometriosis presents a challenging problem to affected women and their gynecologists. As such, there continues to be investigation into the pathogenesis and potential treatments of the condition.

Keywords

Endometriosis • Dysmenorrhea • Pelvic pain • Infertility • Endometrioma • Minimally invasive surgery

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1 Introduction

Endometriosis is a chronic, benign gynecologic condition of reproductive-age women. Approximately 6–10% of premenopausal women are affected by this complex disorder. It is characterized by the presence of endometrial glands and stroma beyond the uterine cavity, occasionally at distant sites. The implantation and proliferation of endometrial cells in distant tissues can cause inflammation, fibrosis, and distortion of normal anatomy. The survival of endometriotic implants in ectopic sites is highly dependent on estrogen, in addition to the local immune response.

Clinically, women affected with endometriosis may experience dysmenorrhea, dyspareunia, pelvic pain, and/or infertility. Endometriosis has been reported in up to 20–50% of infertile women and in 71–87% of women with chronic pelvic pain (ACOG 2010). This chapter will discuss the pathogenesis, evaluation, and treatment of women with endometriosis.

2 Pathogenesis

2.1 Proposed Theories

Endometriosis is a complex disorder that continues to be the subject of research investigation. Several theories have been proposed to explain the pathogenesis of the condition; however, it is likely that no single theory can fully explain the complexities of the disorder (Fritz and Speroff 2011; Schenken et al. 2015).

The oldest and most commonly accepted theory suggests that endometriosis is the result of endometrial glands and stroma migrating into the abdominal cavity via retrograde menstruation through the fallopian tubes. These endometrial cells then attach and implant onto the surface of pelvic organs, where they are resistant to apoptosis and induce local inflammation. The most frequent sites of implantation include the ovaries, anterior and posterior cul-de-sacs, uterosacral ligaments, and broad ligament. Endometriosis found in abdominal scars following a cesarean delivery, or in perineal or vaginal scars following an obstetrical laceration repair, may also be explained by this "implantation theory." However, there is evidence that retrograde menstruation also occurs in women without endometriosis; thus, endometriosis cannot exclusively be explained by this theory.

An alternative theory proposes that endometriosis is the result of metaplasia of multipotent cells found in the peritoneal cavity. Specifically, it is suggested that exposure to menstrual fluid may induce transformation of these multipotent cells into endometriotic lesions. The fact that endometriosis has been diagnosed, although infrequently, in young girls who have not yet started their menstrual cycles, lends support to this particular theory.

A third hypothesis suggests that endometriosis is the result of vascular and/or lymphatic transport of endometrial cells. This may explain endometriosis found in distant organs such as lymph nodes, the thoracic cavity, and the umbilicus. Intriguingly, endometriosis has also been identified in such sites as the bone, lung, breast, and brain.

2.2 Immune Alterations in Endometriosis

There is existing evidence that endometriosis is associated with immune dysfunction (Fritz and Speroff 2008). For example, peritoneal fluid from women with endometriosis demonstrates increased numbers of immune cells. Interestingly, this local inflammatory response appears to promote, rather than suppress, endometriotic lesions. The cytokines and growth factors secreted by these immune cells in turn stimulate attachment and proliferation of the ectopic endometrium. These cytokines include interleukin-1, interleukin-6, interleukin-8 and tumor necrosis factors. Local angiogenesis is promoted by vascular endothelial growth factor (VEGF). There is also evidence for impaired natural killer cell activity in the ability to recognize and act upon ectopic endometrium (Burney and Giudice 2012).

2.3 The Role of Estrogen

It is well documented that endometriosis responds to hormonal stimulation. In particular, the steroid hormone estrogen promotes the survival and growth of endometriotic lesions. In premenopausal women, the ovaries secrete the majority of circulating estrogen; however, estrogen production also occurs in adipose and skin tissue by conversion of androgens to estrogens, via the enzyme aromatase. Intriguingly, in women with endometriosis, estrogen synthesis also appears to occur locally within the endometriotic tissue, further promoting abnormal growth (Burney and Giudice 2012).

2.4 Pathophysiology of Pelvic Pain

Pelvic pain is a common complaint among reproductive-age women. Pelvic pain is complex and multifactorial and is not limited to gynecologic factors. Non-gynecologic etiologies for pelvic pain include the gastrointestinal, urologic, musculoskeletal, psychological, and neurologic systems (Shin and Howard 2011). Chronic pelvic pain can be severe enough to require treatment or cause functional impairment in affected women. In women with endometriosis, pelvic pain is a prominent complaint, thought to be related to the action of prostaglandins, substances involved in inflammation and pain. In women with endometriosis, PGE2 and PGF2a are two specific prostaglandins that are produced in increased amounts in both uterine and ectopic endometrial tissues and may partially explain the pain component of endometriosis.

Pain from endometriosis may also be caused by cyclic bleeding from endometriotic lesions, in a manner that corresponds with a woman's menstrual cycle. Adhesions from endometriosis may distort pelvic anatomy or be located in close proximity to pelvic nerves, also causing alterations in pain sensation and processing.

2.5 Pathophysiology of Infertility

There are several mechanisms underlying the infertility component of endometriosis (ASRM Practice Committee 2012; Macer and Taylor 2012). First, endometriosis may cause distortion of normal anatomy, particularly of the fallopian tubes. The altered anatomic relationships between the ovaries and the fallopian tubes may interfere with oocyte capture after ovulation. Fallopian tubes, which may be blocked at their distal fimbriated ends, may accumulate with serous fluid, causing a distended, swollen tube known as a hydrosalpinx. Hydrosalpinges are a well-known cause of tubal factor infertility. Second, chronic inflammation may interfere with normal endometrial, ovarian, or tubal function. These problems may disrupt follicular development, fertilization of an oocyte, or implantation of an embryo. Further, women with endometriosis often have diminished ovarian reserve or a lower quantity of oocytes remaining than may be expected for age.

2.6 Risk Factors

Risk factors for endometriosis include early menarche (before 11 years old), short menstrual cycles (<27 days), and heavy bleeding during menses. Increased number of pregnancies and duration of lactation, both of which reduce the total number of menstrual cycles in a woman's life, are inversely associated with endometriosis. Interestingly, lower body mass index (BMI) is correlated with increased prevalence of endometriosis. There does not appear to be any racial or ethnic predisposition toward the development of endometriosis; however, a familial association has been observed, with a nearly tenfold increased risk of endometriosis in women with an affected first-degree relative. In addition, women with endometriosis have higher rates of concurrent mood and autoimmune or pain disorders (Sinaii et al. 2002; Smorgick et al. 2013).

3 Clinical Diagnosis

The clinical manifestations of endometriosis vary widely. Many women with endometriosis are asymptomatic, and endometriosis may be

Table 1 Differential diagnoses

Presenting clinical symptom	Differential diagnosis
Dysmenorrhea	Primary dysmenorrhea
	Uterine fibroids (myoma)
	Adenomyosis
	Mullerian anomalies
	Endometritis
	Pelvic inflammatory disease
Pelvic pain	Pelvic inflammatory disease
	Ectopic pregnancy
	Ovarian mass (benign or malignant)
	Ovarian torsion
	Myofascial pain of pelvic floor
	Irritable bowel syndrome
	Interstitial cystitis
	Appendicitis
	Diverticulitis
	Sexual or physical abuse
Pain with intercourse (dyspareunia)	Myofascial pain of pelvic floor
	Sexual or physical abuse
	Vaginal dryness
Infertility	Consider any male or female factor
Ovarian mass	Any benign or malignant ovarian cyst
	Ectopic pregnancy
	Uterine fibroid
	Paratubal cyst
	Dilated fallopian tube (as in pyosalpinx, hydrosalpinx, hematosalpinx)
	Pelvic abscess

incidentally discovered at the time of pelvic surgery. The diagnosis of endometriosis can only definitively be made by surgical excision and histologic confirmation of endometrial glands and stroma outside of the uterine cavity. However, in practice, many women with symptoms of endometriosis are treated empirically, to avoid the risks of diagnostic surgery.

Women with endometriosis may report any of the following symptoms: dysmenorrhea, pelvic pain, dyspareunia, infertility, gastrointestinal issues such as diarrhea or constipation, pain with bowel movements, or pain with urination. Dysmenorrhea in endometriosis tends to develop a few years following menarche. Dyspareunia is usually with deep vaginal penetration, not with superficial pain at the vaginal introitus. Endometriosis-associated pelvic pain varies widely in location and severity and can be described as sharp, dull, localized, or diffuse.

The differential diagnosis of women presenting with any of the above symptoms is quite extensive (Mounsey et al. 2006; Schenken et al. 2013). Other conditions that may be considered in the differential diagnosis are listed in Table 1.

3.1 Patient Evaluation

Work-up of endometriosis includes a thorough history provided by the patient, including an assessment of the duration and severity of her symptoms. The clinician should inquire about the impact of her symptoms on her quality of life. Reproductive goals should also be addressed, as an understanding of a patient's desire for future fertility is crucial to guide treatment options.

Physical examination is also an important diagnostic tool. This includes a thorough abdominal and pelvic examination. On abdominal

examination, palpation of the lower abdominal quadrants may elicit tenderness. In cases of a large ovarian endometriosis cyst, a mass may be appreciated on palpation of the abdomen.

Pelvic examination may demonstrate any of the following: tenderness of the adnexa, uterus, posterior cul-de-sac, or uterosacral ligaments; an adnexal mass (usually unilateral, although may be bilateral); and/or nodularity on the uterosacral ligaments and the rectovaginal septum (Schenken et al. 2015). In severe endometriosis, a "frozen pelvis" may be appreciated on pelvic examination, meaning the pelvic organs are no longer mobile but are instead firmly fixed due to deeply infiltrative disease and adhesions.

It is important to note that there may not be any abnormal findings on physical examination in women with endometriosis. If a patient's history alone is suggestive of endometriosis, it is appropriate to pursue additional diagnostic studies, or even initiate empiric treatment for suspected endometriosis.

3.2 Diagnostic Surgery

The majority of endometriotic implants at the time of diagnostic surgery are identified on the following organs: ovaries, anterior and posterior pelvic cul-de-sacs, posterior broad ligament, uterosacral ligaments, uterus, fallopian tubes, and the sigmoid colon. Less common sites of endometriosis include the bladder and the ureters.

Minimally invasive surgical approaches are the mainstay of diagnosing endometriosis within the abdomen and pelvis, with excellent success in obtaining tissue biopsies for histologic confirmation. On surgical evaluation, the classic appearance of endometriosis is a small, black "powder burn" lesion on the peritoneum, but endometriosis implants can vary widely in appearance. They can appear red and inflamed or white and opacified. They may cause puckering, scarring, or nodularity of the peritoneal surfaces. Due to the varied appearance of endometriosis, histologic confirmation is imperative.

An ovarian cyst containing ectopic endometrium is known as an endometrioma. These cysts contain endometrial tissue with old menstrual blood. Endometriomas may spill fluid that has a "chocolate-like" appearance if they are inadvertently ruptured intraoperatively. Endometriomas are thus also known as "chocolate cysts."

In severe endometriosis, laparoscopic visualization of the pelvis can demonstrate extensive adhesive disease, where peritoneal surfaces are replaced by fibrosis and the pelvic organs are adhered to the cul-de-sac, rectum, bladder, or pelvic sidewalls.

Microscopic evaluation of endometriosis will demonstrate the presence of both endometrial glands and stroma. Unlike normal endometrium, endometriotic tissue may be characterized by the additional presence of blood and fibrous tissue. In one study, endometriosis was confirmed histologically in nearly one-fourth of abnormally appearing peritoneal sites, which were not suspected to be endometriosis at the time of surgery. This reinforces the fact that endometriosis is requires a histopathologic diagnosis (Albee et al. 2008).

3.3 Screening for Endometriosis

There are no good screening tests for endometriosis. CA-125 is a serum marker that is elevated in certain types of ovarian cancer, and within the gynecologic field, CA-125 is primarily used for monitoring of ovarian cancer treatment response. CA-125 may also be elevated in women with endometriosis, especially those with deep infiltrating disease or an endometrioma (Santulli et al. 2015). However, CA-125 is a non-specific marker. It has been shown to be elevated in other conditions causing inflammation of the peritoneal cavity, such as inflammatory bowel disease and liver disease. CA-125 is thus not recommended as a screening tool for endometriosis due to its poor specificity.

Certain radiologic studies can be useful for detection of endometriosis. Pelvic ultrasound, which is generally the first-line imaging study for gynecologic disorders, can detect an endometrioma. On ultrasound, an endometrioma has the classic appearance of dark, hypoechoic fluid

(consistent with blood) surrounded by a bright, echogenic capsule; however, pelvic ultrasounds are not useful for detecting pelvic adhesions or small endometriotic implants. Magnetic resonance imaging (MRI) can also be used for identification of an endometrioma. In addition, MRI can be a useful, noninvasive tool for identifying superficial endometriosis implants, especially if actively bleeding, and can also identify the loss of tissue planes that may occur with severe adhesive disease (de Venecia and Ascher 2015). Thus, although more costly than an ultrasound, MRI may be useful if a more sensitive imaging study is warranted.

4 Classification/Staging of Endometriosis

There are various systems that have been proposed to classify the stages of endometriosis. The most commonly used system was developed by the American Society for Reproductive Medicine (ASRM). The ASRM classification model accounts for the location, size, and depth of endometriotic lesions visualized at the time of diagnostic laparoscopy.

The classification system is summarized as follows (Fritz and Speroff 2008):

Stage 1 (minimal): Isolated superficial peritoneal or ovarian implants. No significant adhesions.

Stage 2 (mild): Superficial peritoneal or ovarian implants, less than 5 cm in total, without significant adhesions.

Stage 3 (moderate): Multiple implants, both superficial and deep. May be associated with adhesions of the ovaries or fallopian tubes. May have partial obliteration of the posterior cul-de-sac.

Stage 4 (severe): Multiple superficial and deep endometriosis implants. Dense adhesions noted. May have complete obliteration of the pelvic cul-de-sac. Large ovarian endometrioma may be present.

The majority of women with endometriosis are diagnosed with stage 1 or 2. Interestingly, there is little correlation between a patient's disease stage and the severity of her pelvic pain symptoms. Disease stage tends to better correlate with a patient's degree of infertility.

5 Treatment of Endometriosis

Goals of treatment for women with endometriosis include pain control, hormonal suppression of active endometriosis, and/or surgical removal or destruction of endometriosis (Vercellini et al. 2014). Therapy must be individualized to a patient's symptoms and her reproductive goals. Therapeutic options for endometriosis are summarized in Table 2.

For those women who do not desire immediate childbearing, and for whom pelvic pain is the primary concern, medical therapy includes analgesic medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs). Hormonal therapy is also used to suppress active endometriosis. Broadly speaking, hormonal treatments are used to suppress the hypothalamic-pituitary-ovarian axis. In doing so, systemic estrogen production is decreased. Up to 70% of women may experience improvement in their pain with hormonal suppression. Commonly used methods in clinical practice include oral contraceptive pills (estrogen and progestin combinations or progestin-only pills), the levonorgestrel-releasing intrauterine device, depot medroxyprogesterone acetate injection, or aromatase inhibitors (Schenken et al. 2013; Taylor et al. 2011). Patients electing to use oral contraceptive pills often benefit from taking them continuously, as opposed to cyclically.

Hormonal treatments also include gonadotropin-releasing hormone (GnRH) agonists. GnRH agonists are used in patients who have not responded to NSAIDs, combined estrogen-progestin therapies, or progestin-only therapies. The goal of GnRH agonist therapy is to reduce ovarian estrogen production to menopausal levels. Upon discontinuation of the medication, ovarian function returns to its normal levels, and its reversibility is why GnRH agonists are favored over surgical removal of the ovaries, especially in young women. However, the use of

Table 2 Treatment of endometriosis

Non-hormonal	Mechanism of action	Indications	Special considerations
NSAIDs (e.g., ibuprofen, naproxen)	Anti-inflammatory	Pelvic pain, dysmenorrhea	Low cost, readily available
Hormonal	Mechanism of action	Indications	Special considerations
Combined estrogen and progestin oral contraceptive pills (OCPs)	Negative feedback on pituitary gonadotropin secretion	Pelvic pain	
	Inhibits ovarian estrogen production	Dysmenorrhea	
Progestin-only therapies	Negative feedback on pituitary gonadotropin secretion	Pelvic pain	Multiple routes of administration (orally, intramuscular, intrauterine)
Depot medroxyprogesterone acetate (intramuscular injection)	Inhibits ovarian hormone production	Dysmenorrhea	
	Inhibits endometriotic tissue growth		
Levonorgestrel-releasing intrauterine device			
Progestin-only pills			
Aromatase inhibitors	Inhibits ovarian estrogen production	Pelvic pain	
	Decreases estrogen production within endometriosis lesions		
Gonadotropin-releasing hormone (GnRH) agonists	Negative feedback on pituitary gonadotropin secretion	Pelvic pain	Expensive; side effects include menopausal symptoms
	Suppresses ovarian function completely	Dysmenorrhea	
Surgical	Goals of surgical intervention	Indications	Special considerations
Excision of endometrioma	Provides diagnostics and therapeutic benefit	Pelvic pain	Laparoscopic approach recommended, depending on size
		Infertility	
		Ovarian mass	

GnRH agonists is only recommended for up to 6 months, due to concerns about bone density loss. In addition, patients who receive GnRH agonists may experience menopausal symptoms, such as hot flushes, vaginal atrophy, and mood swings. There is evidence that "add-back" administration of either a progestin-only, or a combined (estrogen and progesterone) oral contraceptive pill, may prevent or lessen these side effects, as well as preserve bone density, while still providing effective treatment of pelvic pain (Hornstein et al. 2015).

Hormonal suppressive therapies may also be successfully used for the treatment of dyspareunia, dysmenorrhea, or heavy menstrual bleeding. Hormonal suppression is not recommended for women desiring immediate fertility.

Surgical therapy is generally recommended when hormonal suppression is not effective or is contraindicated. If a woman is suspected to have an endometrioma, based on physical examination or an imaging study, she may also benefit from surgical intervention; however, immediate surgery is not always necessary, especially if the patient does not have symptoms. A minimally invasive, laparoscopic approach is a safe and effective way to treat endometriosis surgically. Although, intuitively, it seems as though surgical removal of an ovarian endometrioma would improve fertility rates, there is evidence that ovarian surgery may negatively affect ovarian

reserve in women with endometriosis because of the inadvertent removal of normal ovarian tissue during cystectomy (Somigliana et al. 2012; Vignali et al. 2015). As such, surgical removal of an ovarian endometrioma must be carefully considered in the infertile population and is generally only recommended in symptomatic patients or in patients for whom the endometrioma obstructs their fertility treatment, such as making oocyte retrieval impractical during an in vitro fertilization cycle.

In women without an endometrioma, the goal of surgical intervention is to restore normal anatomy, destroy scar tissue, and to excise or ablate small endometriosis implants. Laser ablation or surgical excision of small endometriotic implants can improve pain symptoms in a majority of women. However, there is a high risk of pain recurrence within 5 years following surgery (Vercellini et al. 2014). In women with mild to moderate endometriosis, laparoscopic treatment of endometriosis may improve pregnancy rates for up to 36 weeks following surgery (Marcoux et al. 1997).

In women who have completed childbearing and who do not desire future pregnancies, definitive surgical treatment may be considered. This includes removal of the uterus (hysterectomy), ovaries, and fallopian tubes (salpingo-oophorectomy). It is important to counsel patients who are considering such surgery that their pain symptoms may recur postoperatively. In premenopausal women who are considering removal of their ovaries, detailed counseling about the risks of premature menopause is also imperative. In addition to the known side effects of menopause, including hot flushes, vaginal atrophy, and mood changes, premature menopause is known to increase a woman's long-term risk of osteoporosis and cardiovascular disease. Unlike in natural menopause, where ovarian function gradually declines, surgical menopause causes an abrupt cessation of hormone production.

In addition, women should be counseled regarding the risk of ovarian remnant syndrome. Ovarian remnant syndrome is defined as the presence of residual ovarian tissue after an oophorectomy, usually unintentionally (Shin and Howard 2011). In women with endometriosis, any remaining ovarian tissue can continue to produce estrogen to stimulate endometriosis implants elsewhere, or within the remaining tissue itself. In addition, the remaining tissue may be at risk for the development of malignancy.

6 Interventions for Endometriosis-Associated Infertility

There are many factors, both male and female, that may contribute to infertility. If a thorough evaluation has been performed, and endometriosis is thought to be an underlying factor, then treatment may be warranted. In women with stage 1 or 2 endometriosis, laparoscopic treatment of endometriosis may modestly improve pregnancy rates. Medical therapy is not recommended for women desiring immediate fertility.

Reproductive specialists may offer more aggressive fertility treatments to women with endometriosis, as they are often observed to have diminished ovarian reserve and decreased oocyte quality. Controlled ovarian stimulation (either with oral or injectable medications), in combination with intrauterine insemination, may increase the chance of pregnancy in women with minimal or mild endometriosis. Medications given for ovarian stimulation are known to increase the risk of multiple gestation pregnancies, especially twins. Multiple gestation pregnancies carry greater risks than singleton pregnancies, and it is important to counsel patients appropriately prior to initiating ovarian stimulation.

In women with moderate to severe endometriosis, their chance of successful pregnancy may be optimized by the use of assisted reproductive technology. In vitro fertilization followed by embryo transfer has been accepted as the most effective approach for pregnancy in these patients. However, the presence of hydrosalpinges from intra-abdominal adhesions is known to impair in vitro fertilization success rates. The mechanism for this is not fully understood, but suggested theories include toxicity of the hydrosalpinx fluid on embryo development and endometrial

receptivity. In women with a known hydrosalpinx, surgical removal or surgical occlusion of the proximal portion of the fallopian tube is recommended prior to proceeding with in vitro fertilization.

7 Natural History of Endometriosis

In women in whom endometriosis is not treated, the condition may progress, regress, or remain stable. In pregnancy, endometriosis symptoms may regress or even disappear, despite the fact that circulating levels of estrogen increase during pregnancy. This is thought to be attributed to pregnancy-related changes on the uterine endometrium. In the postpartum period, lactation induces a low-estrogen state, which may also suppress endometriosis. The symptoms of endometriosis decline as a woman approaches menopause, and endometriosis is quiescent in the postmenopausal state.

There is emerging research regarding the association between endometriosis and certain subtypes of epithelial ovarian cancer (Kim et al. 2014; Sainz de la Cuesta et al. 1996). One proposed mechanism suggests that a small percentage of endometriosis lesions may undergo "malignant transformation" into certain histologic subtypes of ovarian cancer. An alternative hypothesis is that the genetic and immune risk factors that predispose a woman to the development of endometriosis may also increase the risk of ovarian cancer. However, at this time, endometriosis is still considered to be a benign condition and not premalignant.

8 Conclusion

Endometriosis is a benign, but complex, disorder of reproductive-age women. It is characterized by the presence of endometrial stromal and glandular tissue in ectopic sites, beyond the uterus. Affected women may suffer from dysmenorrhea, pelvic pain, and infertility. Medical and surgical treatments are available and must be individualized based on a woman's symptoms and reproductive goals. Endometriosis may have a significant impact on a woman's quality of life, and there continues to be an extensive body of research aimed at understanding this complex disorder.

9 Cross-References

- ▶ Abdominal Hysterectomy: Indications, Avoiding Complications
- ▶ Basic Management of Infertility
- ▶ Gynecologic History and Examination of the Patient
- ▶ Laparoscopic Hysterectomy
- ▶ Laparoscopic Ovarian Cystectomy
- ▶ Management of Pelvic Pain, Dyspareunia, and Endometriosis
- ▶ Pre-op Counseling and Prophylactic Measures in Gynecology

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Diagnosis and Management of Ectopic Pregnancy

Elizabeth Stephens Constance and Molly B Moravek

Contents

Abstract

Ectopic pregnancy is the abnormal location of a pregnancy, outside of the uterus. The most common location of an ectopic pregnancy is the fallopian tube although ectopic pregnancies may also be found in the cervix, interstitial segment of the fallopian tube, ovary, uterine scar from previous cesarean section, or abdominal cavity. The greatest risk to maternal morbidity and mortality associated with ectopic pregnancy is tubal rupture, leading to hemodynamic instability and rapid maternal decompensation. Therefore, early detection and treatment can lead to improved maternal outcomes. Diagnosis of ectopic pregnancy can generally be made using a combination of serial beta HCG monitoring and transvaginal ultrasound. First-line treatment in a stable patient is usually methotrexate. Methotrexate may be administered via a fixed multidose, single-dose, or two-dose regimen in combination with close beta HCG monitoring. For women who fail medical management, in whom medical management is contraindicated, or for whom tubal rupture is suspected, laparoscopic surgery is the treatment of choice. Surgical management may be accomplished by either salpingostomy or salpingectomy, depending on patient characteristics.

Keywords

Ectopic pregnancy • Methotrexate • Discriminatory zone • Pregnancy of unknown location

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1 Introduction

Ectopic pregnancies represent a significant cause of maternal morbidity and mortality. They remain the leading cause of death in women during the first trimester, accounting for 75% of first-trimester maternal deaths and 9–13% of all pregnancy-related deaths (Guven et al. 2007; Barnhart et al. 2007; Banz et al. 2010). With improvements in diagnostic technologies, including human chorionic gonadotropin (HCG) monoclonal assays and high-resolution transvaginal ultrasound (TVUS), the diagnosis can frequently be made early, allowing for more conservative medical and surgical management and improved fertility outcomes. This has caused a subsequent paradigm shift in treatment, away from emergent life-saving surgery and toward outpatient medical management and minimally invasive surgery techniques that better preserve reproductive anatomy and future fertility. Despite these advances, investigation and diagnosis of early pregnancy of unknown location, and specifically ectopic pregnancy, remains a source of uncertainty and therefore stress for both the patient and the provider. This chapter will discuss the pathogenesis, evaluation, and treatment of ectopic pregnancies.

2 Epidemiology

Due to improvements in early detection and a shift toward outpatient management, the true incidence of ectopic pregnancy has become difficult to accurately measure. It is estimated that ectopic pregnancies account for 2% of all pregnancies with 100,000 cases reported each year (Barnhart et al. 2007). Furthermore, ectopic pregnancies account for approximately 9% of all pregnancy-related deaths (Chang et al. 2003). From 1970 to 1992, the incidence of ectopic pregnancies increased sixfold, while during that same time, the risk of death related to ectopic pregnancy decreased by 90% (Goldner et al. 1993).

Two primary factors have contributed to the increasing difficulty in surveillance of ectopic pregnancy in the United States: inpatient treatment of ectopic pregnancies has decreased, and multiple outpatient healthcare visits per ectopic pregnancy have increased (Zane et al. 2002). Therefore, use of hospital discharge diagnosis codes grossly underestimates new diagnoses, while use of coding data from the ambulatory care setting is likely to lead to overestimation of both the incidence and prevalence. Despite these challenges to contemporary surveillance of disease trends, the estimated incidence of ectopic pregnancies since 2002 has remained stable (Hoover et al. 2010). This trend can likely be attributed to the increase in use of ovulation induction agents and assisted reproductive technologies (ART) and simultaneous improvements in prevention and treatment of sexually transmitted infections (STIs), thus decreasing pelvic inflammatory disease, all of which are risk factors for ectopic pregnancy.

3 Pathogenesis

The term ectopic pregnancy can refer to any pregnancy located outside of the uterine cavity. Ninety-seven percent of ectopic pregnancies are located in the fallopian tube with 80% of these occurring in the ampullary region (ACOG 2008; ASRM 2013). Extrauterine pregnancies can occur in other locations as well, including the cervix, interstitial segment of the fallopian tube, uterine myometrium, uterine scar from previous cesarean section, ovary, and the peritoneal cavity (Fig. 1).

Any abnormal anatomic or physiological process that interferes with normal tubal transport of an oocyte from the ovary to the endometrial cavity can lead to ectopic pregnancy. Histological studies show that the presence of chronic inflammation and postinflammatory changes, characterized by findings of chronic salpingitis and salpingitis isthmica nodosa (SIN) on surgical pathology specimens, are associated with increased rates of ectopic pregnancy (Green and Kott 1989). Furthermore, placentation and growth of the ectopic gestation is usually intraluminal, with tubal rupture more often occurring as the result of progressive tubal distension and focal necrosis than direct invasion of trophoblastic tissue into the tubal muscularis (Stock 1991). The ectopic

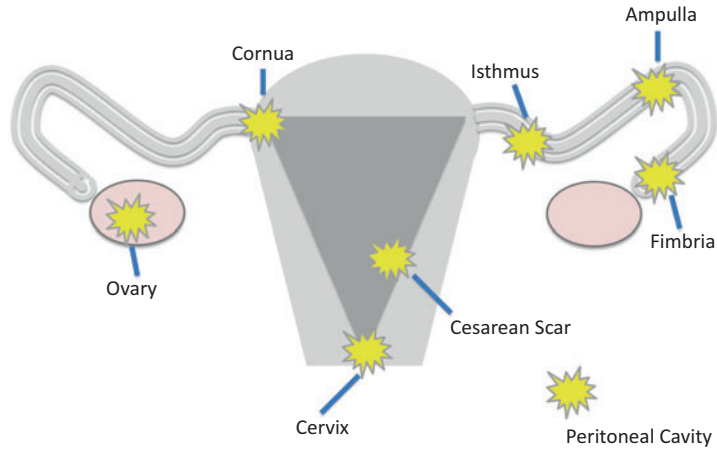

Fig. 1 Sites of ectopic pregnancy

trophoblastic tissue itself may further damage tubal epithelium leading to an increased risk of future, ipsilateral ectopic pregnancy.

4 Risk Factors

While many women presenting with ectopic pregnancy will have a history of one or more well-established risk factors, up to half of affected women will have no such history (ACOG 2008). Risk factors for the development of ectopic pregnancy include (1) history of previous ectopic pregnancy, (2) history of tubal surgery including bilateral tubal ligation (BTL), (3) history of sexually transmitted infection (STI) including tubal infection and pelvic inflammatory disease (PID), (4) history of pelvic surgery and the presence of pelvic adhesions, (5) infertility and use of assisted reproductive technologies (ART), (6) cigarette smoking, (7) current intrauterine device (IUD) use, and (8) in utero exposure to diethylstilbestrol (DES) (ASRM 2013; ACOG 2008).

Recurrent ectopic pregnancy will occur in up to one third of pregnancies following a previous ectopic pregnancy (ACOG 2008). This association is due to a combination of underlying tubal disease leading to the primary event, as well as further tubal damage resulting from its treatment. The number of previous ectopic pregnancies is directly correlated to the risk of recurrence. The odds of developing a subsequent ectopic pregnancy is increased tenfold in women with a history of two previous ectopic pregnancies, compared to women with a history of only one previous event (Skjeldestad et al. 1998). Recurrent ectopic pregnancy is not limited to the ipsilateral fallopian tube. The observation of contralateral recurrence reinforces the theory of chronic inflammation leading to tubal pathology as a primary mechanism of abnormal extrauterine implantation.

An increasingly common source of iatrogenic tubal damage is bilateral tubal ligation (BTL). One third of pregnancies that occur following BTL are ectopic, with post-tubal ligation pregnancies accounting for as many as 10% of all ectopic pregnancies (ACOG 2008). The 10-year cumulative probability of ectopic pregnancy following all methods of tubal sterilization is 7.3 per 1,000 procedures (Peterson et al. 1997). This risk further varies by sterilization method utilized and the woman's age at time of sterilization. Younger age at time of sterilization is associated with an increased risk of lifetime method failure and thus the accompanying risk of ectopic pregnancy. The highest risk of subsequent ectopic pregnancy is associated with sterilization by bipolar tubal coagulation, and the lowest risk is associated with postpartum salpingectomy (31.9 vs. 1.2 ectopic pregnancies per 1,000 procedures, respectively) (Peterson et al. 1997).

Overall, the incidence of ectopic pregnancy is lower for women using any form of contraception compared to women using no contraceptive method at all (Mol et al. 1995). When looking

specifically at ectopic pregnancy risk following contraceptive method failure, concurrent IUD use has the highest association with development of ectopic pregnancy (Furlong 2002). Therefore, any pregnancy in the setting of current IUD use should lead to a high level of clinical suspicion and close surveillance for the presence of an ectopic pregnancy.

Another well-documented cause of anatomic changes to the Mullerian system including tubal pathology is in utero exposure to DES. Associated tubal anomalies include truncated and convoluted fallopian tubes as well as "withered" or constricted fimbriae (DeCherney et al. 1981). These morphologic findings have been associated with up to fivefold increased risk of ectopic pregnancy (Kaufman et al. 2000). Use of DES in pregnancy was banned in 1971 following evidence correlating its use to development of vaginal clear cell adenocarcinoma in exposed offspring. Therefore, potentially affected women are currently reaching the end of their reproductive lifespan; however, this time frame may be extended with increasing availability of ART.

Because early screening and a high level of clinical suspicion can lead to early detection and intervention, counseling of patients with a history of known risk factors for development of ectopic pregnancy is imperative to decreasing associated morbidity and mortality. While in the case of cigarette smoking, lifestyle modification may decrease the risk developing an ectopic pregnancy, for the remainder of patients, presentation early in pregnancy for close monitoring and early documentation of pregnancy location may be beneficial.

5 Diagnosis

Although the incidence of ectopic pregnancies has increased in almost all developed countries, the associated morbidity and mortality have steadily declined due to improvements in early diagnosis (Rabischong et al. 2011). Prompt diagnosis is important for early initiation of appropriate therapy and to reduce the risk of fallopian tube rupture leading to rapid hemodynamic instability. Ectopic pregnancies account for 18% of women presenting to the emergency department with first-trimester bleeding, abdominal pain, or both (ACOG 2008). Because half of women diagnosed with an ectopic pregnancy have no history of associated risk factors, a high level of clinical suspicion should be employed when evaluating any reproductive age woman presenting with vaginal bleeding with or without associated abdominal pain. Although evaluation and diagnosis should be prompt, the finding of an ectopic pregnancy in a hemodynamically stable patient is not always an emergency and can often be treated on an outpatient basis (ASRM 2013).

Both ruptured and unruptured ectopic pregnancies generally present with the classic triad of symptoms: amenorrhea or delayed menses, abdominal pain, and vaginal bleeding (Alsuleiman and Grimes 1982). Pain associated with ectopic pregnancy is generally moderate to severe, lateral, and sharp. Midline pain is associated with decreased risk of ectopic pregnancy (Dart et al. 1999). Other symptoms commonly associated with presentation for ectopic pregnancy are related to tubal rupture and hemoperitoneum. These symptoms include shoulder pain (caused by peritoneal irritation from hemoperitoneum), dizziness, lightheadedness, and shock. Physical exam findings including the presence of peritoneal signs, cervical motion tenderness, and either lateral or bilateral abdominopelvic tenderness have been found to increase the probability of ectopic pregnancy, while uterine size greater than 8 weeks on bimanual exam is associated with decreased likelihood of ectopic pregnancy (Dart et al. 1999). Unfortunately, no combination of signs and/or symptoms has been found that definitively confirm or exclude the diagnosis of ectopic pregnancy; therefore, further testing is required when clinical suspicion is raised.

5.1 Ultrasound

The value and interpretation of transvaginal ultrasound depends on the gestational age of the pregnancy. Accurate gestational age calculation, not

absolute beta HCG level, is the best determinant for when a normal intrauterine pregnancy should be able to be detected by ultrasound (ACOG 2008).

For women with reliable pregnancy dating including those with regular menstrual cycles, a planned pregnancy, or use of ART such as ovulation induction or embryo transfer to achieve pregnancy, predictable findings on ultrasound can confirm normal location and development of the pregnancy. An intrauterine gestational sac is expected to be visible by transvaginal ultrasound between 5.5 and 6 weeks gestational age or 24 days after conception via ovulation induction or embryo transfer (ASRM 2013). Failure to detect an intrauterine gestational sac in the above scenarios is diagnostic of an abnormal pregnancy. Because pregnancy dating is uncertain for many women, failure to identify an intrauterine pregnancy (IUP) on ultrasound usually requires further evaluation with serial HCG levels before a definitive diagnosis of ectopic pregnancy can be made (ACOG 2008).

The beta HCG level at which evidence of a normal intrauterine pregnancy, defined as presence of a gestational sac, is expected to be visible on transvaginal ultrasound is termed the discriminatory zone. The discriminatory zone ranges from 1,500 to 2,500 mIU/mL but will differ by institution depending on the serum assay used and the skill of the ultrasonographer performing the exam (ASRM 2013).

The absence of evidence of an IUP on ultrasound with an HCG level above the discriminatory zone implies an abnormal pregnancy although it does not distinguish between abnormal intrauterine and ectopic pregnancies. Proposals have been made regarding standardization of terminology used when discussing early pregnancy ultrasound findings and are listed in Table 1.

Use of a higher, more conservative, discriminatory zone when making management decisions will decrease the chances of terminating a viable pregnancy (ASRM 2013). Furthermore, it is important to keep in mind that multiple gestation pregnancies will have HCG levels that are higher at earlier stages than singleton pregnancies, but the rate of increase should be similar. Given the presence of increased HCG levels earlier in gestation, the standard discriminatory zone will often be inaccurate for multiple gestation pregnancies. Therefore, a normal pregnancy as indicated by a normal rise in serial beta HCG levels should be followed expectantly until a definitive diagnosis of intra- versus extrauterine pregnancy can be made.

Table 1 Standard terminology for ultrasound findings in early pregnancy

Definite ectopic pregnancy – extrauterine gestational sac with yolk sac and/or embryo (+/− cardiac activity)
Probable ectopic pregnancy – inhomogenous adnexal mass or extrauterine sac-like structure
Pregnancy of Unknown Location (PUL) – no signs of either ectopic pregnancy or IUP
Probable IUP – intrauterine echogenic sac-like structure
Definite IUP – intrauterine gestational sac with yolk sac and/or embryo (+/− cardiac activity)

Barnhart et al. (2011)

Finally, the presence of an IUP does not definitively exclude the existence of a concomitant ectopic pregnancy. A heterotopic pregnancy is defined as the presence of intrauterine and extrauterine pregnancies simultaneously (ACOG 2008). While heterotopic pregnancies are rare, making up less than 1% of all pregnancies, the incidence is increasing with increased use of ART (ACOG 2008). Therefore, clinical suspicion should be maintained when the patient's presentation or symptoms are suggestive of ectopic pregnancy even in the presence of a documented IUP.

5.2 Serial Beta HCG

When the initial beta HCG level is below the discriminatory zone, serial HCG measurements are required to differentiate a potentially viable pregnancy versus a nonviable pregnancy (ASRM 2013). The minimum HCG rise of a potentially viable pregnancy is 53% every 2 days

(ASRM 2013). This minimum rate of rise is lower than previously suggested and is based on the 99% confidence interval around the mean of the curve for HCG rise (ASRM 2013). Use of this more conservative value further prevents possible termination of a viable pregnancy, as discussed above.

As long as the minimum rise is achieved, serial HCG monitoring can continue until the discriminatory zone is reached, at which time ultrasound should be performed to confirm pregnancy location. A declining or abnormally rising HCG level indicates an abnormal pregnancy. After a spontaneous abortion, HCG levels are expected to decline at least 21–35% every 2 days, although an appropriately declining HCG does not exclude the possibility of ectopic pregnancy or rupture (ASRM 2013).

5.3 Uterine Curettage

The absence of a gestational sac above the ultrasound discriminatory zone, in association with an abnormally rising or declining HCG level, confirms the diagnosis of abnormal pregnancy of unknown location (PUL) (ASRM 2013). In this situation, it is important to distinguish between ectopic pregnancy and abnormal IUP for the purpose of selecting the appropriate treatment course.

Uterine curettage can be used to make this important distinction. The presence of chorionic villi on tissue pathology following uterine curettage simultaneously makes the diagnosis of abnormal intrauterine pregnancy while providing definitive surgical treatment (ACOG 2008). On the other hand, absence of chorionic villi on tissue pathology with a persistent abnormally rising HCG following uterine curettage establishes the diagnosis of ectopic pregnancy (ASRM 2013). Due to the need to await results of tissue pathology, which often takes several days, this course of action is only appropriate for hemodynamically stable patients able to be monitored in an outpatient setting. Endometrial biopsy is insufficient for diagnosis of pregnancy location in the setting of PUL and should not be considered an appropriate alternative for uterine curettage (ASRM 2013).

6 Treatment

6.1 Expectant Management

Women wishing to forgo medical or surgical therapy in favor of expectant management should be appropriately counseled regarding the risks of tubal rupture and hemorrhage, including warning signs requiring further evaluation. Appropriate candidates for expectant management include women who are asymptomatic, have early tubal gestations, and have objective evidence of pregnancy resolution as indicated by low baseline and decreasing HCG levels (ACOG 2008). The likelihood of success of expectant management has been shown to correlate with beta HCG level, with success rates of 98%, 73%, and 25% associated with beta HCG levels of <200, <500, and $>2{,}000$ mUI/mL, respectively (Yao and Tulandi 1997). The US Centers for Disease Control and Prevention (CDC) does not track data regarding rates of treatment with expectant management; therefore, population-based data on its use and efficacy are lacking (CDC 1995). Given the risk associated with method failure, expectant management should not be the preferred method except in asymptomatic patients with a low and already falling beta HCG level.

6.2 Medical Management with Methotrexate

With improved diagnostic modalities leading to earlier diagnosis of ectopic pregnancies prior to tubal rupture, the standard of care for treatment has moved away from surgical interventions toward increased use of conservative medical management. Methotrexate has become widely accepted as the primary treatment for ectopic pregnancy (ASRM 2013). Although methotrexate is not FDA approved for this use, its use is supported by multiple professional organizations including the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM).

Methotrexate is well studied in pregnancy as the result of its use in the treatment of gestational trophoblastic neoplasia (GTN) since 1956 (ACOG 2008). It was first used to treat ectopic pregnancies in 1982 (ACOG 2008). Long-term data has shown no association with congenital anomalies in future pregnancies (ACOG 2008). In addition, there is currently no evidence to suggest any adverse effect of methotrexate therapy on subsequent fertility or ovarian reserve (ASRM 2013).

Medical management is more cost-effective than surgical management and achieves similar outcomes (Barnhart et al. 2007). Randomized trials comparing the use of methotrexate to fallopian tube-sparing laparoscopic surgery show no difference in overall tubal preservation, tubal patency, repeat ectopic pregnancy, or future fertility (ACOG 2008). Methotrexate, therefore, has the additional benefit of avoiding surgery and its associated complications without compromising efficacy or successive reproductive outcomes.

6.2.1 Mechanism of Action

Methotrexate is an antimetabolite that works by interrupting DNA synthesis and repair, as well as cell replication (ACOG 2008). Folic acid is normally reduced to tetrahydrofolate by the enzyme dihydrofolate reductase (ASRM 2013). Methotrexate is a folic acid antagonist that acts by binding to the catalytic side of dihydrofolate reductase, interrupting the synthesis of purine nucleotides and the amino acids serine and methionine (ACOG 2008). It affects rapidly proliferating tissues including bone marrow, buccal and intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue (ACOG 2008). Therefore, the associated side effects are also at the level of rapidly dividing cells and tissues.

6.2.2 Adverse Effects

The most common side effects reported are GI symptoms including nausea, vomiting, and stomatitis (ACOG 2008). Alopecia is associated with higher doses of methotrexate but is uncommon at the treatment doses used in the setting of ectopic pregnancy (ACOG 2008). Methotrexate is known to be directly toxic to hepatocytes and is cleared by the renal system; therefore, women being treated with methotrexate should be advised to abstain from both alcohol and NSAIDs during treatment. Women should also be counseled to avoid prolonged sunlight exposure due to increased skin sensitivity and to refrain from sexual intercourse and vigorous exercise during treatment due to risk of tubal rupture. In addition, women should be instructed to discontinue prenatal vitamins and folic acid supplementation prior to and during methotrexate administration, as these can reduce the effectiveness of treatment (ASRM 2013).

Whenever possible, definitive diagnosis of an ectopic pregnancy should be made prior to initiating medical therapy. In addition to medication side effects, potential consequences of medical management of a presumed ectopic pregnancy include (1) subsequent pregnancies being viewed as high risk for recurrent ectopic pregnancy resulting in repeated, costly, and anxiety-provoking diagnostic evaluation; (2) apparent efficacy of methotrexate to treat ectopic pregnancy will be artificially increased; and (3) risk of exposing an IUP to a known teratogen and abortifacient potentially resulting in embryopathy (ASRM 2013).

6.2.3 Candidates for Medical Therapy

The identification of appropriate candidates for outpatient medical management is imperative to treatment success and risk reduction. Candidates for medical management should demonstrate (1) hemodynamic stability, (2) absence of severe or persistent abdominal pain, (3) commitment to outpatient follow-up until resolution is achieved, (4) normal baseline liver and renal function tests, and (5) an unruptured mass (ASRM 2013; ACOG 2008). Absolute and relative contraindications to medical management are listed in Table 2.

6.2.4 Laboratory Evaluation

Before deciding to proceed with methotrexate therapy, women should undergo appropriate testing including CBC (demonstrating no evidence of bone marrow dysfunction indicated by significant

Table 2 Contraindications to methotrexate therapy

Absolute contraindications	Relative contraindications
Blood dyscrasias including leukopenia, thrombocytopenia, or significant anemia	Gestational sac >3.5 cm
Breastfeeding	Embryonic cardiac activity detected by TVUS
Chronic liver disease including alcoholism and alcoholic liver disease	Initial HCG concentration >5,000 mUI/mL
Hemodynamic instability	Refusal to accept blood transfusion
Immunodeficiency	Inability to participate in outpatient follow-up
Intrauterine pregnancy	
Peptic ulcer disease	
Pulmonary disease	
Renal dysfunction	
Rupture ectopic pregnancy	
Sensitivity to methotrexate	

ACOG (2008), ASRM (2013)

anemia, leukopenia, or thrombocytopenia), LFTs, creatinine, and blood type with Rh status (ASRM 2013; ACOG 2008). Women who are Rh negative necessitate treatment with RHOGAM in the presence of any vaginal bleeding. These blood tests are typically repeated 1 week after treatment to evaluate for any adverse effects of medical therapy on renal, hepatic, or hematologic function (ACOG 2008). Elevation of transaminase levels are most commonly seen with multidose regimens and usually resolve within 1–2 weeks of completion or discontinuation of therapy (ACOG 2008). Women with a history of pulmonary disease should have a chest x-ray prior to treatment due to the risk of interstitial pneumonitis in the setting of underlying lung disease (ASRM 2013). Because of this rare but serious risk, all women should report any fever or respiratory symptoms that develop following treatment (ACOG 2008).

6.2.5 Multidose Regimen

Three separate methotrexate administration regimens have been described in the literature and include fixed multidose, singe-dose, and two-dose options. The fixed multidose regimen has been used for treatment of ectopic pregnancy the longest (Barnhart et al. 2007). This treatment regimen alternates methotrexate 1 mg/kg on treatment days 1, 3, 5, and 7 with leucovorin (folinic acid) 0.1 mg/kg on treatment days 2, 4, 6, and 8 (ACOG 2008). The use of a folinic acid "rescue" on alternating days serves to reverse the effects of methotrexate thereby reducing the side effects associated with large doses (Barnhart et al. 2007). This alternating regimen is continued until the beta HCG level falls by at least 15% from the peak concentration, and as many as 50% of women will not require the full 8 days of treatment (ASRM 2013). Once an initial 15% decline in HCG is obtained, HCG monitoring should be continued weekly until a negative result is achieved. Complete HCG resolution usually takes 2–3 weeks but may take up to 6–8 weeks (ASRM 2013) (Fig. 2).

6.2.6 Single-Dose Regimen

The single-dose regimen is the simplest treatment course available. It was developed in response to pitfalls of the multidose regimen, in order to reduce side effects, increase convenience of administration, and eliminate the need for folinic acid rescue (Barnhart et al. 2007). This regimen consists of administration of methotrexate 50 mg/m^2 on treatment day 1 followed by monitoring of HCG levels on treatment days 4 and 7. If a minimum 15% decrease in HCG is observed between treatment days 4 and 7, no further treatment with methotrexate is required, and HCG levels should be monitored weekly until negative. If a 15% decrease in HCG is not observed, a second dose of MTX 50 mg/m^2 should be administered on treatment day 7 with HCG monitoring repeated on days 4 and 7 after the second dose (ACOG 2008). Up to 20% of women undergoing treatment with this regimen will require a second dose of methotrexate (Barnhart et al. 2007). This can be repeated as necessary; however, failure to obtain a 15% decrease in HCG after two doses should prompt consideration of surgical management (ACOG 2008). An initial rise in HCG may be observed on treatment day 4 in relation to the

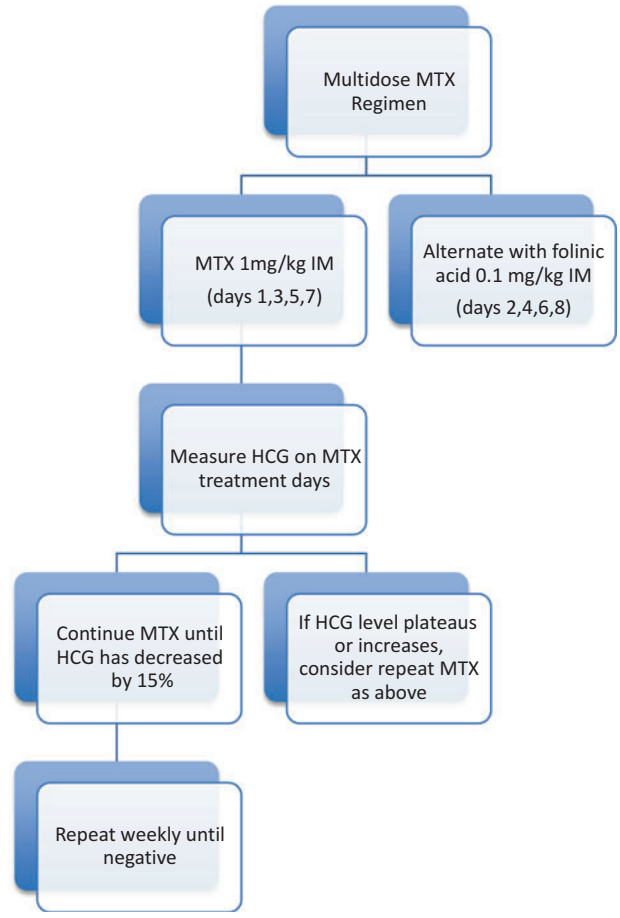

Fig. 2 Multidose methotrexate regimen

pretreatment baseline HCG and should not be a cause for concern (ACOG 2008). If, during the course of follow-up, HCG levels plateau or increase, repeat administration of methotrexate may be warranted (ACOG 2008) (Fig. 3).

Review of several observational studies show a failure rate of 14.3% or higher with the single-dose regimen when pretreatment HCG levels exceed 5,000 mIU/mL, compared to a failure rate of only 3.7% when the starting HCG level is below 5,000 mIU/mL (ACOG 2008). Other studies have suggested an increased failure rate of the single-dose regimen at even lower HCG levels, above 1,300 mIU/mL (Rabischong et al. 2011). Therefore, patients with higher initial HCG levels should be appropriately counseled regarding the potential need for more than one dose of methotrexate and possible treatment failure.

6.2.7 Two-Dose Regimen

The two-dose regimen was developed to serve as a compromise between the previous regimens detailed above. The goal of this regimen is to maximize the number of doses administered without the need for folinic acid rescue while minimizing the number of medical visits required and optimizing patient convenience and treatment efficacy (Barnhart et al. 2007). This regimen consists of the administration of methotrexate 50 mg/m^2, on each of treatment days 0 and 4, for a total of two doses. An HCG level is then obtained on treatment day 7. If a decline in HCG of at least 15% compared to the pretreatment value is achieved, no further methotrexate administration is required, and HCG levels are monitored weekly until negative. If the decline in HCG on treatment day 7 is less than 15% of the pretreatment level, a

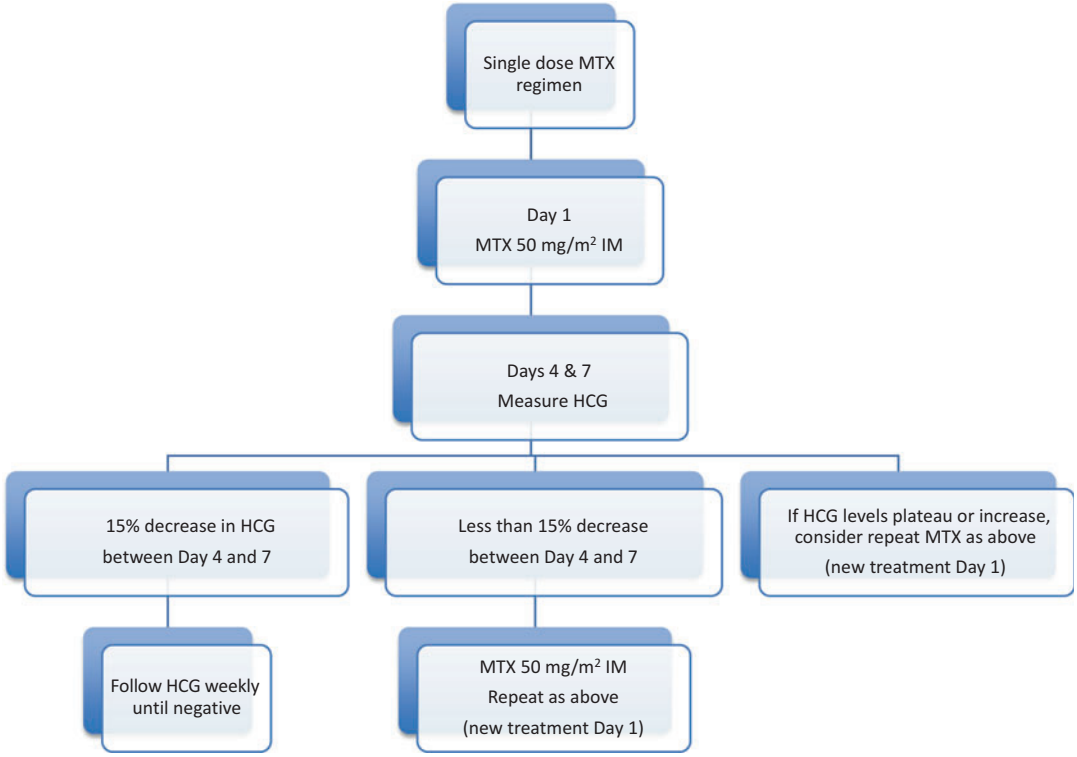

Fig. 3 Single dose methotrexate regimen

third dose of methotrexate is administered on treatment day 7 and the HCG level reevaluated on treatment day 11. If a 15% decline in HCG is still not achieved, a fourth dose is administered on treatment day 11 and the HCG level repeated on treatment day 14. Failure to obtain at least a 15% decline in HCG by treatment day 14 warrants discontinuation of medical therapy and consideration of surgical management (Fig. 4).

Laboratory evaluation including CBC, LFTs, and creatinine should be performed on treatment day 7, at the time of administration of the third and fourth doses of methotrexate if required, and 2 weeks posttreatment (Barnhart et al. 2007). Methotrexate administration should be discontinued if at any point in the treatment process the patient is found to have LFTs greater than 50% above the upper limit of normal, white blood cell count $<3 \times 10^9$/L, or platelet count $<100{,}000$.

When choosing which of the above treatment regimens to use, treatment efficacy should be weighed against potential morbidity of repeat methotrexate dosing. A meta-analysis comparing the efficacy of the multidose versus single-dose regimens demonstrated that the single-dose regimen was less effective (88.1%) than the multidose regimen (92.7%) (ACOG 2008). The failure rate for the single-dose regimen remained statistically significantly higher even after controlling for initial HCG level and the presence of embryonic cardiac activity (Barnhart et al. 2007). However, subsequent papers have shown no difference in failure rates between these two treatment regimens (Rabischong et al. 2011). Furthermore, a prospective study evaluating the efficacy of the two-dose regimen demonstrated high patient satisfaction and few side effects (Barnhart et al. 2007). This study demonstrated an overall success rate of 87.1% with 72% of patients requiring a single two-dose course and only 5% requiring a total of four doses. Therefore, the risk of treatment failure should be balanced with the ease of medication administration and improved medication adherence with fewer doses when choosing a treatment regimen.

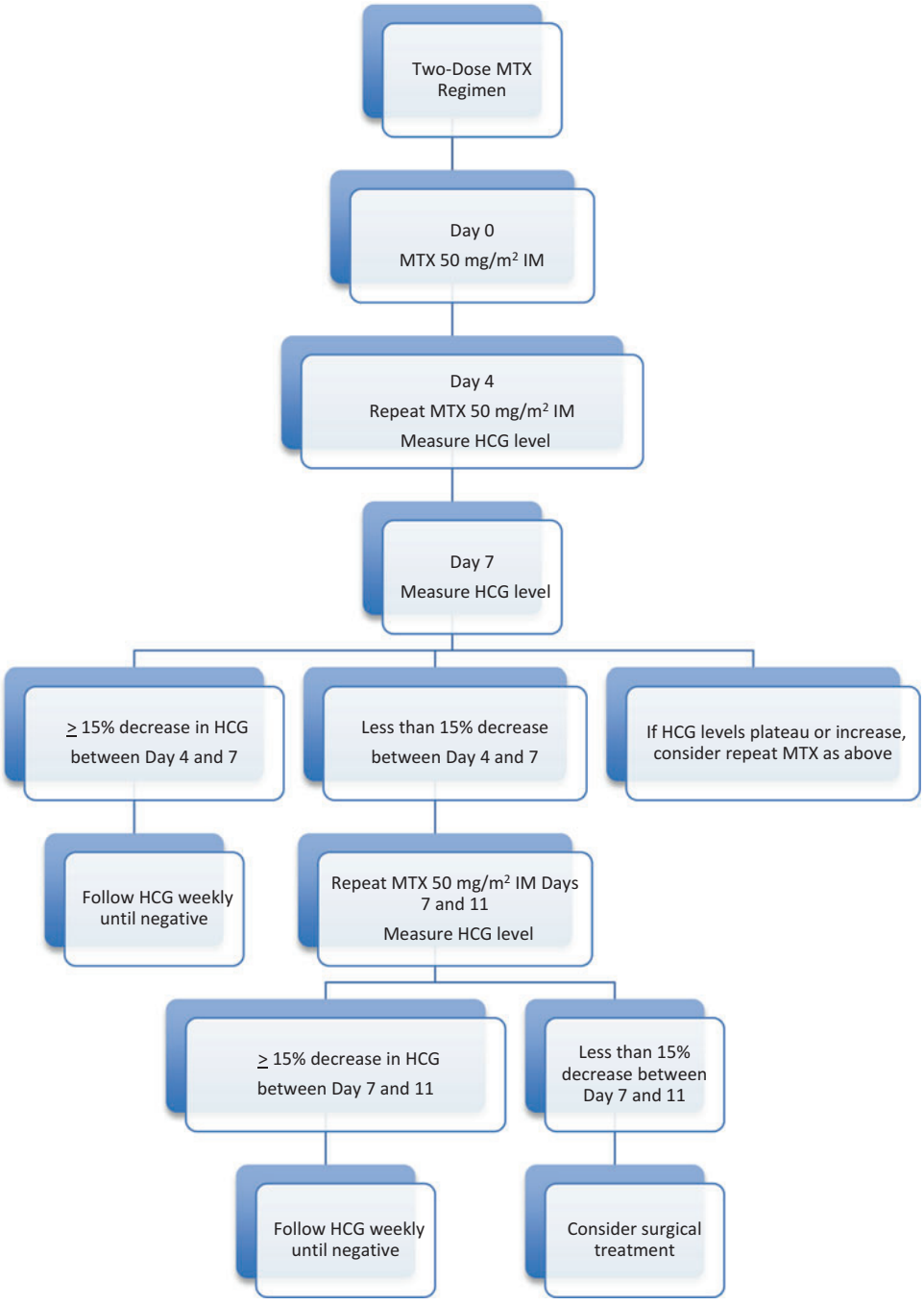

Fig. 4 Two-dose methotrexate regimen

6.2.8 Posttreatment Monitoring

With any of the above treatment regimens, once the initial HCG decline of 15% is achieved, serial HCG levels should be monitored weekly until negative. If at any time in the monitoring process the HCG level is found to increase or plateau, the diagnosis of persistent ectopic pregnancy should be made (ACOG 2008). Tubal rupture can still occur despite declining HCG levels; therefore, clinical suspicion should remain high until a

negative HCG level is obtained. Signs of treatment failure or suspected rupture that are indications to proceed with surgical management (ASRM 2013) include hemodynamic instability, increasing pain regardless of HCG level, and rapidly increasing HCG level >53% in 2 days after four doses of the multidose or two doses of the single-dose regimen (ASRM 2013). Serial ultrasound exams are not necessary nor are they recommended during posttreatment monitoring. Ultrasound findings cannot predict or prove treatment failure unless evidence of tubal rupture is noted (ASRM 2013).

Some patients will develop transient pain following administration of methotrexate regardless of the treatment regimen used. This pain, often referred to as "separation pain," generally occurs 2–7 days following methotrexate administration (ASRM 2013; ACOG 2008). The pain is likely caused by the cytotoxic effect of the medication on trophoblastic tissue causing tubal abortion and generally resolves within 4–12 h after its onset (ACOG 2008; ASRM 2013). In the absence of other signs and symptoms of overt tubal rupture, such as hemodynamic instability or significant hemoperitoneum on ultrasound, this pain can be managed expectantly and does not necessarily indicate a surgical emergency. For pain that is severe and/or persistent, evaluation of serial vital signs and hematocrit levels is warranted. Exploratory surgery should be undertaken if at any time tubal rupture is suspected or the patient becomes hemodynamically unstable.

6.3 Surgical Management

Due to rapid advances in minimally invasive surgical technologies, laparoscopic surgery is currently the gold standard for surgical management of ectopic pregnancy over open laparotomy (Rabischong 2010). The two existing techniques of tubal surgery for removal of ectopic pregnancies are tubal-sparing salpingostomy or complete salpingectomy. The decision of which technique to employ depends both on surgeon preference and patient characteristics.

6.3.1 Salpingectomy

Salpingectomy is the complete surgical removal of the affected fallopian tube. This technique allows for nearly certain removal of the abnormal pregnancy in its entirety. It also removes the damaged fallopian tube, excluding the possibility of a repeat ectopic pregnancy in that same fallopian tube in the future. If the woman retains a normally functioning fallopian tube on the contralateral side, she remains capable of achieving spontaneous pregnancy in the future. It is important to note that a normal appearance of the unaffected fallopian tube at the time of surgery does not guarantee normal function. Therefore, even with a history of treatment with salpingectomy, women with a previous ectopic pregnancy should still be treated as high risk for recurrent ectopic pregnancy in the contralateral tube in future pregnancies.

6.3.2 Salpingostomy

Salpingostomy consists of making a single 10–15 mm incision along the antimesenteric portion of the fallopian tube at the point of maximal bulge from the ectopic pregnancy. The pregnancy tissue is then removed using a combination of aspiration, irrigation, and traction. The tubal incision is subsequently left open to heal by secondary intention in lieu of suturing. This technique may be more cost-effective and result in improved future fertility rates compared to salpingectomy (Rabischong et al. 2010). The primary risk associated with salpingostomy is the incomplete removal of all trophoblastic tissue. It has been estimated that 5–20% of women will experience a persistent ectopic pregnancy following laparoscopic salpingostomy (ACOG 2008). A population-based study looking at 3,196 ectopic pregnancies diagnosed from 1992 to 2008 found that 6.6% of women undergoing laparoscopic salpingostomy required subsequent treatment for persistent ectopic pregnancy; however, that rate increased to 8.6% when the preoperative HCG level was greater than 1,960 IU/L (Rabischong et al. 2010). A prospective study following 289 patients 9 years after treatment of ectopic pregnancy found that, of those that underwent laparoscopic salpingostomy, 18.9% experienced

a repeat ectopic pregnancy in a subsequent pregnancy with 42.9% occurring on the side of previous salpingostomy (Banz et al. 2010).

6.4 Adjunctive Use of Methotrexate

The presence of persistent ectopic pregnancy following surgical treatment with laparoscopic salpingostomy can be treated with a single-dose of adjunctive methotrexate (ASRM 2013). One randomized trial of 129 women demonstrated that empiric administration of a single-dose of methotrexate immediately following laparoscopic salpingectomy essentially eliminated the risk of subsequent persistent ectopic pregnancy (Graczykowski and Mishell 1997). However, due to the relatively low incidence of persistent ectopic pregnancy following salpingostomy, many women would need to be treated to prevent one persistent ectopic pregnancy. Therefore, use of HCG monitoring postoperatively in order to identify those who would benefit most from subsequent methotrexate administration is the preferred strategy (ACOG 2008).

7 Conclusions

Ectopic pregnancy remains a significant cause of maternal morbidity and mortality in the first trimester. Therefore, all reproductive age women presenting for vaginal bleeding with or without abdominal pain should be tested for pregnancy, and ectopic pregnancy should be included in the differential diagnosis. Advances in serum beta HCG assays and high-resolution transvaginal ultrasonography allow for earlier diagnosis of ectopic pregnancy, leading to improvements in management options. When initial ultrasound fails to provide a definitive diagnosis regarding pregnancy location, serial beta HCG levels may be followed until the ultrasound discriminatory zone is reached. Uterine curettage may also be utilized to provide a definitive diagnosis in cases of abnormal pregnancy of unknown location. Whereas surgery has historically been the primary treatment for ectopic pregnancy, earlier detection prior to tubal rupture now allows for more conservative medical management with methotrexate in the outpatient setting as the first-line therapy when appropriate. Although multiple treatment regimens exist, close follow-up is warranted to ensure adequate treatment regardless of which regimen is utilized. For those patients in whom medical management fails or is contraindicated, laparoscopic surgery with either salpingostomy or salpingectomy is recommended for definitive treatment.

8 Cross-References

- ▶ Abnormal Vaginal Bleeding During the Early Reproductive Years
- ▶ Anatomy of the Female Genital System
- ▶ Contraception and Family Planning
- ▶ Diagnosis and Management of Gestational Trophoblastic Disease
- ▶ Diagnosis and Management of Pregnancy Loss
- ▶ Management of Acute pelvic Pain: Torsion, Rupture of Ovarian Mass
- ▶ Pelvic Inflammatory Disease and Other Upper Genital Infections

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Diagnosis and Management of Pregnancy Loss

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Abstract

Recurrent pregnancy loss (RPL) is a multifactorial condition encompassing physical and emotional burdens. Several risk factors contribute to spontaneous miscarriage, most commonly through previous history and chromosomal abnormalities. Other etiologies include uterine anomalies, immunologic and endocrine factors, thrombophilias, and environmental pathogens. However, approximately half of all patients with spontaneous pregnancy loss have no reason for these miscarriages (ACOG practice bulletin, 2001). Those who experience two or more consecutive losses warrant further evaluation. Assessment of each patient starts with a comprehensive history and physical examination, karyotype testing, imaging of the pelvic structures, and detailed medical workup of possible conditions. If a definite cause is identified, treatment is focused on correcting the abnormality. Psychological support may be crucial and even therapeutic; patients should be comforted that a subsequent live birth is possible with great success.

Keywords

Recurrent miscarriage • Spontaneous abortion • Pregnancy loss • Antiphospholipid syndrome • Aneuploidy

1 Introduction

Sporadic pregnancy loss is common, occurring in approximately 15–25% of all pregnancies (Hatasaka 1994). Normally, a miscarriage is not an anticipated event, and couples go through emotional, physical, and traumatic experiences as a result of this occurrence. Recurrent pregnancy loss is one of the more challenging and difficult aspects of reproductive medicine. According to the American Society for Reproductive Medicine (ASRM), recurrent pregnancy loss is a distinct disorder defined by two or more failed clinical pregnancies documented by ultrasonography or histopathological examination and not necessarily consecutive (Practice Committee of ASRM 2013). The European Society for Human Reproduction and Embryology (ESHRE) defines RPL as three consecutive losses, not necessarily intrauterine (Kolte et al. 2015). At very early gestational ages (<10 weeks), most losses, whether sporadic or recurrent, result from chromosomal errors (Wilcox et al. 1988; Practice Committee of ASRM 2012). As a result of increased prevalence of numerical chromosomal abnormalities with advancing maternal age, the prevalence of miscarriage increases with aging: <30 years of age (9–17%), at age 35 years (20%), at age 40 years (40%), and at age 45 years (80%). About 2% of pregnant women experience two consecutive miscarriages, while <1% experience three or more (Nybo Andersen et al. 2000). This chapter evaluates the etiology, evaluation, and treatment of recurrent pregnancy loss.

2 Etiology

Studies investigating RPL have identified several attributing factors including genetic, thrombophilic, anatomic, immunological, endocrine, infectious, and environmental causes. The overall risk of miscarriage in the first pregnancy is 11–13%, and this risk increases to 14–21% in the subsequent pregnancy after one miscarriage (Stirrat 1990). Advancing maternal age is associated with increased rates of pregnancy loss. Patients in this age group tend to have higher meiotic chromosomal errors and increased risk of aneuploidy, which contributes to higher rates of losses. In fact the sporadic miscarriage rate approaches 50% in patients above the age of 40 (Dunson et al. 2002).

2.1 Genetic Factors

More than half of all early pregnancy losses are associated with chromosomal abnormalities. Aneuploidies such as trisomies and monosomies are the most common chromosomal number errors found in sporadic miscarriages (Goddijn et al. 2004). Triploidies, or the duplication of an

Table 1 Classification criteria for the diagnosis of antiphospholipid syndrome (Adapted from ACOG Practice Bulletin No. 132 with permission)

APS is present in one of the following clinical criteria and one of the following laboratory criteria are met
Clinical criteria
1. Vascular thrombosis
2. Pregnancy morbidity
(a) One or more unexplained deaths of morphologically normal fetuses after the 10th week of gestation by ultrasound or direct examination of the fetus
(b) One of more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe preeclampsia or recognized features of placental insufficiency
(c) Three or more unexplained consecutive spontaneous abortion before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded
Laboratory criteria
1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart
2. Anticardiolipin antibody of IgG or IgM isotype in serum or plasma present in medium or high titer (>40 GPL or MPL or >99th percentile), on two or more occasions at least 12 weeks apart
3. Anti-β_2 glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile), present on two or more occasions at least 12 weeks apart

entire set of chromosomes, have been implicated in RPL as well. Other chromosomal anomalies include chromosomal rearrangements such as balanced translocations, reciprocal (60%) and Robertsonian (40%), which are observed in about 2–5% of couples with recurrent miscarriages (Franssen et al. 2005). These are more common in female fetuses, and translocations of maternal origin are more likely to result in pregnancy loss as compared to those of paternal origin. Less common chromosomal rearrangements consist of inversions. Recurrent pregnancy loss as a result of chromosomal anomalies is more common with: young maternal age at second miscarriage and/or a positive family history of two or more miscarriages (Goddijn et al. 2004).

2.2 Thrombophilic Factors

Pregnancy induces a hypercoagulable state as a physiologic mechanism to prevent postpartum bleeding. Fibrinogen and thrombin levels increase, while protein S decreases. Additionally, changes in hormone levels cause venous stasis as a result of enhanced compliance of the vessel walls. Procoagulant microparticles, such as procoagulant aminophospholipids, phosphatidylserine, and phosphatidylethanolamine, may contribute to the hypercoagulable state and as such may interfere with successful implantation and fetal growth. Microparticles also cause apoptosis, platelet activation, and endothelial stimulation leading to increased incidence of pregnancy loss (Laude et al. 2001).

Although data on fibrinolytic factors and the effect of recurrent pregnancy loss is sparse, there seems to be a direct association between factor XII deficiency and RPL. In studies, women with recurrent miscarriage have shown decreased levels of factor XII activity and prolonged activated partial thromboplastin time. Decreased factor XII activity contributes to reduced fibrinolysis, increasing the likelihood of thrombosis (Sotiriadis et al. 2007).

2.3 Immunological Factors

During pregnancy there is a state of immune tolerance toward the fetus and placenta. When there is insufficient tolerance, spontaneous abortion or infertility may ensue. Embryos contain both maternally and paternally derived antigens. Paternal antigens and immunomodulatory factors present in semen are not recognized by the mother and are protected by trophoblasts. When the blastocyst is abnormal, paternal antigens are exposed, creating an immune response from the mother. Allogenic factors are thought to cause RPL in a

similar fashion to a transplanted graft rejection (Hill and Choi 2000).

One particular immunological response that can contribute to RPL is the presence of antiphospholipid antibodies. Antiphospholipid syndrome (APS) is the only immune condition in which pregnancy loss is a diagnostic criterion for the disease. Five to twenty percent% of patients with recurrent pregnancy loss will test positive for antiphospholipid antibodies (Parke et al. 1991). Diagnosis of antiphospholipid syndrome is outlined in Table 1 (ACOG practice bulletin, 2001). These antibodies react directly with phospholipids; they affect the trophoblast by inhibiting villous cytotrophoblast differentiation and extravillous cytotrophoblast invasion into the decidua, inducing syncytiotrophoblast apoptosis, and initiating maternal inflammatory pathways on the syncytiotrophoblast surface. The decidua becomes infiltrated with tumor necrosis factor alpha (TNF-α) levels, complement C3, and neutrophils (Hill and Choi 2000). Overall, this alters the immune cell prolife at the maternal-fetal interface, causing pregnancy loss (Tong et al. 2015).

2.4 Anatomic Factors

Congenital uterine anomalies are present in 2.7–16.7% of the general population (Devi et al. 2006). Relevant Müllerian tract anomalies include unicornuate, didelphic, bicornuate, septate, or arcuate uteri. Septate uterus, however, is the most common anomaly associated with pregnancy loss (Homer et al. 2000). In such case, spontaneous abortions may be related to impaired uterine distention or abnormal implantation. Alternatively, decreased vascularity, increased inflammation, or reduction in sensitivity to hormones in the defect may affect implantation.

Depending on their location, leiomyomas may alter the uterine cavity and impede implantation. This may be due to multiple factors including poor endometrial receptivity of the decidua overlying the myoma or due to degeneration and subsequent cytokine release. Submucosal leiomyomas are more commonly associated with recurrent pregnancy loss (Simpson 2007).

Intrauterine adhesions are created from granulation tissue after trauma to the basalis layer. The connective tissue formed may adhere to the uterine walls, creating a physical barrier to implantation in the uterine cavity. Also known as Asherman's syndrome, this anatomic deformity may lead to recurrent pregnancy loss (Pabuçcu et al. 1997).

2.5 Endocrinologic Factors

There appears to be an association between abnormal thyroid levels and pregnancy loss, mainly high serum thyroid antibody concentrations (thyroid peroxidase or thyroglobulin). Although no direct cause has been identified, excess thyroid hormone increases the risk of miscarriage (Stagnaro-Green et al. 2004; Bellver et al. 2008).

Poorly controlled diabetes mellitus causes hyperglycemia, maternal vascular disease, and adverse autoimmune factors. High values of hemoglobin A1C (values above 8%) increase the incidence of congenital fetal malformations and the frequency of miscarriage (Ylinen et al. 1984). Women with well-controlled blood sugars are not at an increased risk of spontaneous abortion (Mills et al. 1988).

Women diagnosed with polycystic ovarian syndrome (PCOS) have a higher miscarriage rate compared to the general population (20–40% vs. 10–20%) (Glueck et al. 2002). PCOS is known to be caused by sex hormone abnormalities leading to premature or delayed ovulation, poor endometrial receptivity, and disturbances in synthesis, secretion, and action of prostaglandins and ovarian growth factors. Serum luteinizing hormone levels, testosterone levels, and androstenedione concentrations are all elevated, causing adverse effects on the endometrium. Pregnancy loss is increased as a result of alterations in these hormone levels (Rai et al. 2000).

Normal levels of prolactin aid in maintaining early pregnancy and women with high circulating prolactin levels have higher rate of recurrent miscarriages. Hyperprolactinemia may cause alterations in the hypothalamic-pituitary-ovarian axis, resulting in impaired folliculogenesis and oocyte maturation (Hirahara et al. 1998).

Successful implantation and maintenance of pregnancy requires progesterone (Practice Committee 2015). A possible but unproven cause of impaired progesterone production is a defect in corpus luteum function, also known as luteal phase defect, which leads to failure of development of a fully mature secretory endometrium (Practice Committee to ASRM 2015). Altered levels of progesterone may cause spontaneous abortions. Several underlying conditions including high prolactin levels and abnormal thyroid function may lead to diminished levels of progesterone (Daya et al. 1988).

2.6 Infectious Factors

Many pathogens including *Listeria monocytogenes*, *Toxoplasma gondii*, *Chlamydia trachomatis*, Ureaplasma *urealyticum*, *Mycoplasma hominis*, *Cytomegalovirus*, and herpesvirus among others may lead to sporadic miscarriages. However, there is no evidence proving that infections with these agents lead to recurrent pregnancy loss (Matovina et al. 2004). It is possible that an active infection may destabilize the balance of tolerance and rejection mentioned earlier in early pregnancy. That imbalance may cause multiple pregnancy losses in the form of rejections.

2.7 Male Factors

Sperm aneuploidy and DNA fragmentation are the main abnormalities found in sperm. Abnormal DNA fragmentation is present with advanced paternal age and exposure to certain environmental factors (exogenous heat, varicoceles, increased reactive oxygen species in semen, and toxic exposures). However, cytogenetically abnormal sperm may be selected against during fertilization through routine conception (Gopalkrishnan et al. 2000).

2.8 Lifestyle, Environmental, and Chemical Factors

Cigarette smoking, obesity, alcohol consumption, illicit drug use, and caffeine intake have been associated with miscarriages. These factors seem to relate to pregnancy loss in a dose-dependent fashion. Smoking in particular has an adverse effect on trophoblastic function. Chemicals including anesthetic gases, arsenic, aniline dyes, benzene, ethylene oxide, formaldehyde, pesticides, lead, mercury, and cadmium are associated with sporadic spontaneous pregnancy loss (Christiansen et al. 2005).

3 Evaluation

Since spontaneous miscarriage can be a common, sporadic event, evaluation of patients for recurrent pregnancy loss should be initiated after two consecutive miscarriages or one second trimester loss. Evaluation must begin with a detailed history and physical examination with detailed description of all medical conditions, previous surgeries, and genetic and family disorders. Details of each previous pregnancy such as gestational age and isolated characteristics must be evaluated in addition to constructing a three-generation pedigree to identify possible heritable traits. Physical examination should be comprehensive with attention to pelvic organ abnormalities and signs of endocrinopathies (Christiansen et al. 2005). Due to the increased association of chromosomal abnormalities and miscarriage, some have argued that RPL evaluation should be selective rather than universal and only performed if the products of conception of the second miscarriage were euploid. Changes toward use of selective RPL evaluation seem to have more cost savings compared to universal evaluation (Foyouzi et al. 2012).

3.1 Genetic Assessment

In addition to obtaining a detailed history with a three-generation pedigree, karyotyping of couples is part of the evaluation for RPL. Parental karyotypes detect translocations or mosaic patterns that might be passed down to the fetus. Major chromosomal abnormalities are five to six times more likely to be detected in couples experiencing recurrent pregnancy loss than in the general population. Once identified as having a structural chromosomal rearrangement, affected couples may consider the option of assisted reproductive technologies with preimplantation genetic testing. Preimplantation genetic diagnosis (PGD) for specific translocations and then transfer of unaffected embryos or the use of donor gametes result in successful pregnancies in the absence of other identifiable cause of RPL.

Chromosomal analysis of the products of conception is of significant clinical value despite not being part of the initial RPL workup. An abnormal fetal karyotype may give psychological alleviation to the experiencing couple as the identifiable cause of the sporadic abortion. Normal karyotype in the products of conception may suggest maternal environmental factor as the cause of the spontaneous abortion. The possibility of maternal tissue contamination is present if cytogenetic analysis (G-banding karyotype) yields 46,XX karyotype. In these situations, reflex DNA extraction and microsatellite analysis of maternal blood can differentiate fetal versus maternal DNA, whereas SNP microarray technology is able to differentiate maternal versus fetal DNA in the products of conception. If karyotyping is not available, placental histology identifying trophoblast inclusions suggests genetic defects (De Braekeleer et al. 1990).

3.2 Thrombophilia Assessment

Inherited thrombophilias might be the cause of recurrent pregnancy loss, especially with evidence of placental ischemia and infarction and maternal vessel thrombosis. Screening for factor V Leiden, prothrombin gene mutations, and other thrombophilias is justified with a positive personal history of venous thromboembolism or first-degree relative with high-risk thrombophilia (Practice Committee of ASRM 2012). If confirmed with thrombophilia, anticoagulant therapy with unfractionated heparin or low-molecular-weight heparin may be started immediately after conception.

Acquired thrombophilias such as antiphospholipid antibodies syndrome has a strong correlation with RPL as discussed earlier. The diagnosis is made on the basis of clinical vascular thrombosis or pregnancy morbidity along with laboratory findings of anticardiolipin antibody (IgG and IgM) and lupus anticoagulant (Table 1.). Serum tests for anticardiolipin antibody and lupus anticoagulant should be repeated 6–8 weeks apart to ensure no false-positive values due to viral illnesses. Lupus anticoagulant is detected based on an activated partial thromboplastin time, kaolin plasma clotting time, or dilute Russell viper venom test time. Standard treatment of patients diagnosed with APS consists of low-dose aspirin and heparin.

3.3 Anatomic Assessment

Müllerian anomalies are typically detected using sonohysterography and hysterosalpingography (HSG). Both methods provide additional information compared to sonography alone. Sonohysterograms delineate the internal contours of the uterine cavity while also providing visualization of the outer wall of the uterus. Additionally, sonohysterogram can distinguish between a septate and bicornuate uterus (Keltz et al. 1997). Hysterosalpingograms provide detailed information about the tubal anatomy and patency, similar to the sonohysterogram. However, an HSG cannot evaluate the outer contour of the uterus. In the recent years, the emergence of the three-dimensional ultrasound has proven to be an excellent noninvasive method for evaluating anatomic anomalies. In a comparison performed by Jerkovic and colleagues, the use of three-dimensional ultrasound identified the same congenital anomalies compared to

hysterosalpingography (Jurkovic et al. 1995). Szkodziak and colleagues further concluded that three-dimensional transvaginal ultrasound might become the optimal method to diagnose uterine anomalies (Szkodziak et al. 2014). Detailed characterization of uterine defect may be identified with the use of magnetic resonance imaging (MRI), which allows for visualization of both uterine cavity and the external contour of the uterus, thus distinguishing septate from bicornuate uteri (Soares et al. 2000). Hysteroscopy and laparoscopy provide direct visualization of uterine anomalies with the additional benefit of correcting these anomalies as they are diagnosed, however both procedure are invasive compared with the aforementioned modalities. Hysteroscopy remains the gold standard for diagnosing and treating intrauterine lesions that may hinder embryo implantation.

3.4 Endocrine Assessment

Maternal endocrine disorders are usually routinely evaluated. Screening women for thyroid dysfunction is reasonable due to emerging associations with increased miscarriage risks and thyroid abnormalities. In the presence of elevated thyroid stimulating hormone (TSH) levels above 2.5 mIU/L, screening for antithyroid antibodies should be performed (Negro et al. 2010).

The presence of thyroid peroxidase (TPO) autoantibodies and anti-thyroglobulin antibodies increases the spontaneous miscarriage risk two to three times higher than those without these antibodies (even in euthyroid women). Recommendations for levothyroxine use toward treating patients with euthyroid or subclinical hypothyroid states and positive antithyroid antibodies are being favored (Thangaratinam et al. 2011).

Prolactin is another hormone routinely measured during the initial workup for recurrent pregnancy loss along with ovulatory dysfunction. If hyperprolactinemia is diagnosed, underlying cause such as a prolactinoma should be evaluated. Treatment with a dopamine agonist (bromocriptine) to normalize prolactin levels improves pregnancy outcomes in those with recurrent pregnancy loss. Elevated prolactin may also result in a short luteal phase, diagnosed as luteal phase defect. In the past, endometrial biopsy (EMB) was used to diagnose luteal phase defect; however, histology is not reproducible, and thus EMB is no longer recommended for diagnosis. In those with suspected luteal phase defect, progesterone supplementation is beneficial with a history of three or more consecutive pregnancy losses.

4 Management

Although most therapeutic recommendations are based on clinical experience and data from observational studies, prognosis for successful future pregnancy is good. Goal of treatment depends on the underlying cause of RPL. Regardless of intervention, emotional support is important and, at times, will enhance therapeutic success.

4.1 Karyotype Abnormalities

The first step after diagnosis of chromosomal abnormalities of either parental or fetal origin is genetic counseling. The probability of future chromosomally normal and abnormal conception in addition to carriers of the chromosomal defect should be discussed. The magnitude of each specific chromosomal abnormality varies.

Prenatal genetic studies, including amniocentesis, chorionic villus sampling, and preimplantation genetic testing, all of which can determine fetal karyotype, however, cannot exclude the possibility of certain microdeletions. In vitro fertilization with preimplantation genetic diagnosis (PGD) can be used to transfer unaffected embryos. This treatment modality improves pregnancy outcome for translocation carriers with a history of RPL (Otani et al. 2006). If maternal or paternal chromosomal abnormalities are present, conception of an affected embryo can be bypassed using gamete donation, surrogacy, or adoption. This method of treatment depends on parental preference.

4.2 Thrombophilia

Aspirin given with heparin appears to improve pregnancy outcome in women with antiphospholipid syndrome. Current recommendations are to begin low-dose aspirin when conception is attempted and add prophylactic dose of unfractionated heparin or low-molecular-weight heparin once intrauterine pregnancy is confirmed. Anticoagulation improves maternal outcome in those with certain inherited thrombophilias up to 80% (Bates et al. 2012). However, those with thrombophilias still have an increased risk of complications relating to the pregnancy including preterm birth, preeclampsia, and fetal growth restriction.

4.3 Anatomic Abnormalities

Surgery is the best option for uterine abnormalities that are treatable (uterine septum, intrauterine adhesions, submucosal myoma). Several studies showed improved live birth rates in those surgically treated for the presence of a uterine septum, most easily done hysteroscopically. Performing a hysteroscopic metroplasty can double the incidence of live birth rate (Mollo et al. 2009). For women with irreparable uterine defects, a gestational carrier is an alternative option.

4.4 Endocrine Abnormalities

Women with elevated serum thyroid peroxidase antibody concentrations have higher rates of spontaneous abortion as mentioned earlier. These patients have higher risks of developing hypothyroidism in the first trimester and autoimmune thyroiditis during the postpartum period. Therapy with levothyroxine in euthyroid women with high TPO antibodies may reduce the risk of miscarriage from 13.8% to 3.5% (Negro et al. 2006). Diabetic women with poor glycemic control have a higher incidence of miscarriage than those with tight control. It is thus recommended to achieve a normal glycemic in diabetic patients with RPL.

Prolactin levels during early pregnancy are significantly higher in those with recurrent miscarriage compared to the general population. In one study, 64 women with RPL and hyperprolactinemia who were randomized to treatment with bromocriptine or no bromocriptine, those receiving the dopamine agonist, had higher rates of successful pregnancy (82% vs. 52%) (Hirahara et al. 1998). Bromocriptine is thus recommended as treatment for RPL in women with hyperprolactinemia.

5 Conclusion

Recurrent pregnancy loss can be an emotional and physically traumatic occurrence. Many women suffer from feelings of guilt and self-blame, which may persist in subsequent pregnancies. The majority of miscarriages are due to abnormalities in chromosome numbers. Uterine anomalies, endocrine dysfunction, immunologic disease, thrombophilic disorders, and environmental factors are the remaining causes of pregnancy loss. A full workup for recurrent pregnancy loss is warranted after two miscarriages or one second trimester loss. Emerging reports suggest that a full RPL workup should be obtained only if the second miscarriage is chromosomally euploid; however, further research is needed before this approach becomes routinely adopted (Foyouzi et al. 2012). Although many times a specific cause of the pregnancy loss goes unknown, successful treatment and resulting pregnancies lead to patient satisfaction and overwhelming gratitude.

6 Cross-References

- ▶ Basic Management of Infertility
- ▶ Management of Recurrent Pregnancy Loss
- ▶ Workup and Management of Polycystic Ovary Syndrome

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Management of Acute Pelvic Pain: Torsion, Infection, and Rupture of Tubal or Ovarian Mass

Youssef Mouhayar and Michael Saad-Naguib

Contents

Abstract

Acute pelvic pain is a common complaint in women. Various underlying gynecologic and non-gynecologic pathologies can cause acute pelvic pain; thus, a thorough investigation must be undertaken in order to reach a correct diagnosis. Etiologies include ovarian torsion, ectopic pregnancy, tubo-ovarian abscess, and ruptured ovarian cysts. It is critical to correctly diagnose the etiology of the pelvic pain in order to properly manage the pathology. Depending on the underlying condition, there are many treatment options, including medical and surgical management.

Keywords

Pelvic pain • Ovarian torsion • Ectopic pregnancy • Tubo-ovarian abscess • Hemorrhagic cyst

1 Introduction

Acute pelvic pain is an event that results from various gynecologic or non-gynecologic conditions. Many of these conditions can be managed medically, while others could be life threatening and require surgical intervention. In this chapter, the most common pathologies and their treatment options are reviewed.

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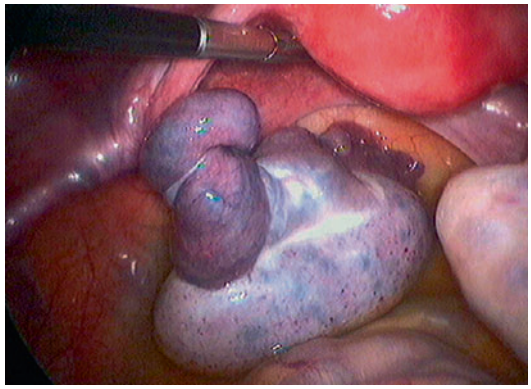

Fig. 1 Ovarian torsion

2 Ovarian Torsion: Etiology and Risk Factors

Ovarian torsion is the partial or complete twisting of an ovary around its ligamentous supports (the infundibulopelvic and utero-ovarian ligaments) (Fig. 1) that can result in disruption of the blood supply to the ovary. Torsion is an uncommon cause of acute pelvic pain, with a prevalence of 2.7% (Dupuis and Kim 2015) affecting women of all ages. Due to the nonspecific nature of the pain caused by ovarian torsion and the consequences of delayed diagnosis, it is critical to quickly and accurately diagnose torsion in order to conserve ovarian function. The biggest concern associated with ovarian torsion is the complete occlusion of the blood supply that can result in necrosis, infarction, hemorrhage, and loss of ovarian function (Dupuis and Kim 2015). Approximately 60% of torsion cases occur in the right adnexa (Schraga et al. 2016).

The most likely causes of ovarian torsion in adult females are benign masses such as functional cysts or corpus lutea. In addition, any neoplasm increases the likelihood of torsion, with increasing risk as the size of the neoplasm increases. Torsion can also occur in normal ovaries without any risk factors; however, it is not well understood how it occurs. When ovarian torsion occurs in a normal ovary, it is more likely to occur in premenarchal females as the utero-ovarian ligament is longer in premenarchal females as it shortens as they go through puberty (Schraga et al. 2016; Karayalçın et al. 2011). In fact, it has been noted that 50% of patients with ovarian torsion who were younger than 15 years old had ovaries with no apparent pathology (Barnhart et al. 2003).

Ovarian masses, especially if $\geq$5 cm, remain the biggest risk factor for torsion. These masses are usually associated with the menstrual cycle or reproductive hormones, thus increasing the risk of torsion in reproductive age women. Another major risk factor for torsion is the size of the ovary. When it is 5 cm or more in diameter, the risk of torsion increases significantly as shown by a series of case studies where it was reported that 83–93% of torsed ovaries were noted to be 5 cm or larger (Tulandi 2015). Women undergoing ovulation induction during infertility treatment are also at an increased risk for torsion due to the presence of large follicular cysts and ovarian enlargement. In patients undergoing infertility treatment who present with acute abdominal pain, nausea and vomiting, and large polycystic ovaries, it is important to consider the possibility of torsion (Dupuis and Kim 2015). Pregnancy, associated with torsion in approximately 20% of torsion cases, and history of pelvic surgery, primarily tubal ligation, are also risk factors for ovarian torsion.

3 Ovarian Torsion: Presenting Symptoms

Patients with ovarian torsion present with acute, moderate to severe pelvic pain and can also have nausea and vomiting (Karayalçın et al. 2011). The main signs and symptoms seen in patients with ovarian torsion in descending order are: pelvic pain (90%), adnexal mass (86–95%), nausea and vomiting (47–70%), abnormal vaginal bleeding (4%), and fever (2%) (Karayalçın et al. 2011). Clinically patients often complain of sudden unilateral lower abdominal pain with onset after exercise or an agitating movement although history and physical findings are highly variable. In contrast to adults with ovarian torsion, infants with torsion may present with feeding intolerance,

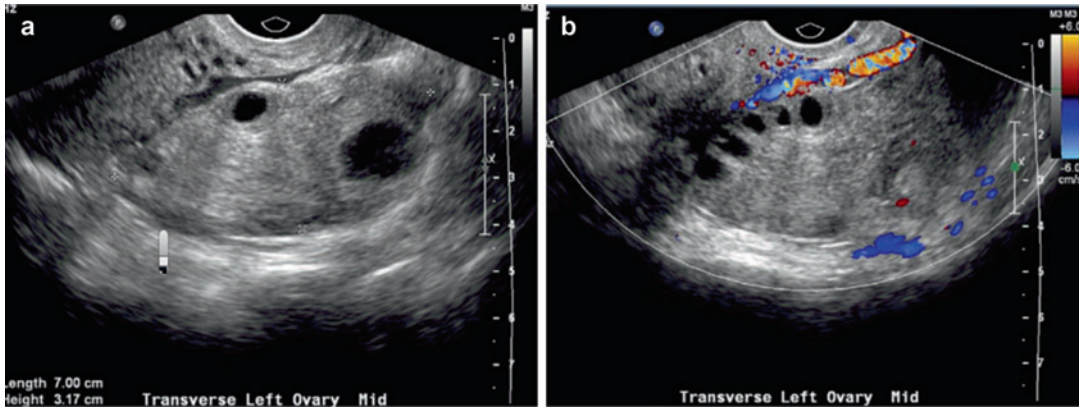

Fig. 2 Gray-scale (**a**) and color (**b**) sonograms of ovarian torsion show an enlarged ovary with prominent peripherally located follicles. The ovarian parenchyma is heterogeneous, and on color images there is a complete lack of parenchymal blood flow (Dupuis and Kim 2015)

vomiting, abdominal distension, and general irritability (Barnhart et al. 2003).

On physical examination, patients may have abdominal or pelvic tenderness, with or without a palpable pelvic mass. In the setting of peritoneal signs, adnexal necrosis might be present, and thus is it critical to reach the correct diagnosis quickly.

4 Ovarian Torsion: Workup and Treatment

Workup of a patient with suspected ovarian torsion should include serum β-hCG level to exclude an ectopic pregnancy, complete blood count (CBC) to monitor for leukocytosis in the setting of adnexal necrosis, and a complete metabolic panel (CMP). Unfortunately, no lab value is specific for ovarian torsion. Imaging, however, may be beneficial in the diagnosis of torsion. It must be noted that while imaging is beneficial, ovarian torsion is a clinical diagnosis. Ultrasound is the initial and preferred imaging method used to detect ovarian torsion, due to its cost-efficiency and diagnostic accuracy (Karayalçın et al. 2011). There are many characteristic ultrasonographic signs that can assist in the diagnosis of torsion such as a heterogeneous appearance of the ovarian stroma due to edema and hemorrhage:

- Decreased or absent Doppler flow within the ovary may be present as seen in Fig. 2b; however, the presence of flow to the ovary does not rule out torsion due to dual blood supply to the ovary (Dupuis and Kim 2015). The blockage of venous blood flow results in engorgement of the parenchyma and edema and that causes the ovaries to enlarge.
- On ultrasound, this can appear hypoechoic with prominent and peripherally located non-ovulatory follicles (Dupuis and Kim 2015).
- Ultrasound was found to have a sensitivity and specificity of 72.1% and 99.6% for torsion, while the positive and negative predictive values were 96.9% and 95.9%, respectively (Swenson et al. 2014).
- Alternatively, magnetic resonance imaging (MRI) and computerized tomography (CT) scan may be utilized; however, they are not as preferable as ultrasonography due to the time consumption and high cost associated with these modalities (Tulandi 2015).

Although imaging is important for diagnosing ovarian torsion, definitive diagnosis is only made via direct visualization. A minimally invasive surgical approach is preferred, unless there is a suspicion for ovarian or fallopian tube malignancy. During surgery, the main goal should be to

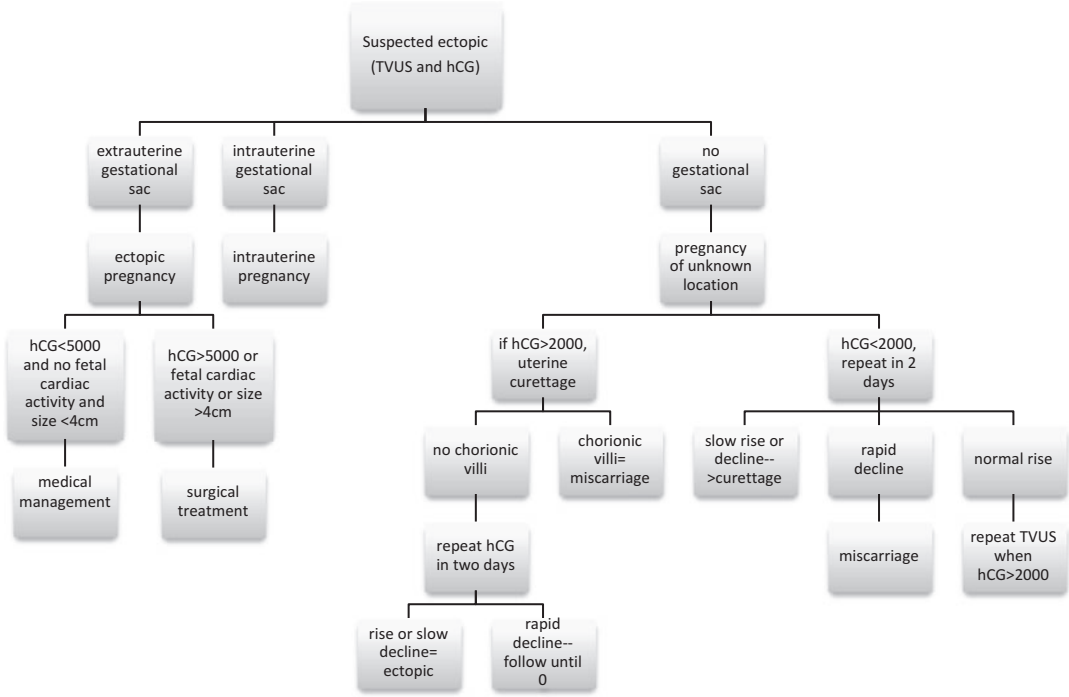

Fig. 3 Management of suspected ectopic pregnancy (Figure 1 from Fritz and Speroff 2010)

determine the presence of ovarian torsion and, if present, to assess the viability of the tube and ovary (Swenson et al. 2014). An ovary that is blue or black in color is not necessarily nonviable; however, dark color and enlargement with vascular and lymphatic congestion most likely indicate nonviability (Swenson et al. 2014).

In children with ovarian torsion, ovarian conservation is recommended regardless of the intraoperative findings. This approach helps to preserve potential fertility and avoids the negative physical, social, and emotional impact on children due to loss of ovarian function (Barnhart et al. 2003).

In premenopausal patients, it is recommended that a conservative approach of untwisting the adnexa and preserving the ovary should be considered particularly where symptoms to surgery is less than 44 h (Karayalçın et al. 2011).

If it is clear that the ovary is necrotic or if there is a mass suspicious for malignancy, then salpingo-oophorectomy should be performed and a gynecologic oncology consultation should be made (Swenson et al. 2014). In postmenopausal women, salpingo-oophorectomy is usually the preferred route of treatment (Swenson et al. 2014).

After conservative treatment of ovarian torsion, there are several options available to prevent recurrence. In the setting of ovarian cysts, high-dose oral contraceptive pills (OCPs) may be used to suppress cyst formation although research support for this is lacking. Oophoropexy, which is fixation or suspension of the ovary, is another option that could be performed at the time of surgery. This procedure is often performed in children with ovarian torsion or in women who had undergone an oophorectomy on the contralateral side due to prior ovarian torsion (Beigi 2015b). However, there is not enough data to support this practice, and further research is needed in order to establish treatment protocols (Swenson et al. 2014).

5 Ectopic Pregnancy

An ectopic pregnancy is a pregnancy which implants outside of the uterine cavity. While the majority (98%) occur in the fallopian tube, other possible sites of implantation are the cervix, uterine cornua, ovaries, and abdomen (Pfeifer et al. 2008). Risk factors for ectopic pregnancy include previous ectopic pregnancy, fallopian tube damage, pelvic inflammatory disease, pelvic adhesions, tubal surgery, current intrauterine device (IUD) use, and assisted reproductive technologies (ART) (Pfeifer et al. 2008). Immediate workup of a possible ectopic pregnancy includes a positive pregnancy test and serum quantitative β-hCG, followed by a thorough history. Fig. 3 demonstrates further workup of possible ectopic pregnancy. Patients with ectopic pregnancy may have various clinical presentations. Although not specific, the most common manifestations of ectopic pregnancy are vaginal bleeding with abdominal or pelvic pain (Pfeifer et al. 2008). Abdominal examination may be unremarkable but it may also demonstrate significant tenderness. Speculum exam should be performed to assess for cervical dilation and to quantify the amount of bleeding; this is followed by bimanual examination, where patients may exhibit cervical motion tenderness with or without an adnexal mass. If there is evidence of hemodynamic instability, such as tachycardia or hypotension, in the setting of a suspected ectopic pregnancy, then surgical exploration is warranted.

After the initial evaluation is completed and hemodynamic stability of the patient is ascertained, then accurate diagnosis of a suspected ectopic pregnancy should follow a certain algorithm. Quantitative β-hCG and ultrasound are used in conjunction to guide in patient management. If the gestational age of the fetus is greater than five and half weeks, then a transvaginal ultrasound (TVUS) can identify an ectopic pregnancy with near 100% accuracy (Fylstra 2008). Another important concept in the diagnosis of a suspected ectopic pregnancy is the discriminatory zone, the β-hCG level at which a normal intrauterine pregnancy can be visualized using ultrasound. With the advances in gray-scale ultrasonography, TVUS can determine the presence of an intrauterine pregnancy (IUP) with a β-hCG value between 1,500 and 2,500 IU/L.

When the β-hCG level is above the discriminatory zone, but no intrauterine pregnancy is detected by TVUS, a dilation and curettage of the uterus is suggested to evaluate for the presence of chorionic villi (Fylstra 2008). If chorionic villi are not detected, then this is considered to be a pregnancy of unknown location and is subsequently treated as an ectopic pregnancy. Alternatively, β-hCG levels may be followed and should demonstrate a minimum drop of 15%. Within 12–24 h in cases of failing IUP. If this is not the case, then an ectopic pregnancy is most likely the diagnosis (Fylstra 2008). On the other hand, when the β-hCG level is below the discriminatory zone, the value should then be serially monitored for appropriate rise as long as the patient is hemodynamically stable. β-hCG levels normally rise by 53% over a 48 h period (Fylstra 2008). The previously used value of 66% increase was determined to be unsafe as it could result in the termination of possible viable pregnancies. In these situations, a TVUS should be performed as soon as the β-hCG level is above the discriminatory zone. A decline or an inappropriate rise of the β-hCG levels indicates a nonviable pregnancy. A β-hCG level that does not decline by 21–35% over 48 h is indicative of an ectopic pregnancy rather than a spontaneous abortion and should be treated as such. MRI might aid in the diagnosis of an ectopic pregnancy when ultrasonography is equivocal. An ectopic pregnancy usually appears as a structure with a "three rings." The affected tube usually demonstrated solid components with dilation and evidence of hematosalpinx as well as enhancement of tubal wall (Rosen et al. 2009).

Treatment options for ectopic pregnancy include expectant, medical, or surgical management and vary according to different clinical scenarios. Expectant management can be offered to patients with pregnancy of unknown location or when there is concern for an ectopic pregnancy in the setting of low or decreasing β-hCG. A β-hCG that is over 2,000 IU/ml is a contraindication for expectant management, and patients should be

treated medically with methotrexate (MTX) or surgically (Fylstra 2008). Medical management with MTX is offered to hemodynamically stable patients without severe or persistent pain and without relative or absolute contraindications to MTX therapy (Teng et al. 2003). Methotrexate is administered as a single dose, double dose, or fixed multidose with serial β-hCG measurements depending on each specific protocol (Teng et al. 2003). Surgical management is reserved for when there is evidence of hemodynamic instability or contraindication for MTX therapy.

A minimally invasive approach is preferred unless there is concern for hemodynamic shock and large hemoperitoneum or when there is suspicion for multiple adhesions or if the pregnancy is extratubal or intra-abdominal (Fylstra 2008). Both, a laparoscopic and an open technique, are equally effective; however, laparoscopy is associated with less blood loss and shorter hospital stay.

Decision to perform a salpingectomy or salpingostomy is usually made intraoperatively depending on the status of the tube. If the tube is ruptured or severely damaged, salpingectomy is preferred as tubal function might be compromised; however, the number of performed salpingostomies has been declining with an increase in in vitro fertilization (IVF) cycle success (Fylstra 2008). While both salpingostomy and salpingectomy procedures yielded a similar subsequent intrauterine pregnancy rates, there was a higher rate of subsequent ectopic pregnancy in patients who had a salpingostomy (10% vs. 15%) in some but not all reports (Fylstra 2008). Treatment with salpingostomy may also fail if the trophoblastic tissue is not completely resected from the tube, in which case the β-hCG levels must be monitored to ascertain their decline to normal.

Future reproductive outcomes appear to be similar after either medical or surgical treatment. It has been shown that the risk of a repeat ectopic pregnancy in patients with previous ectopic is about 10%, regardless of whether the patient underwent MTX treatment or salpingostomy; these patients should be closely monitored for signs and symptoms of ectopic pregnancy (Tulandi 2015).

5.1 Tubo-ovarian Abscess

Tubo-ovarian abscesses (TOAs) are inflammatory masses that involve the fallopian tube, ovary, and adjacent organs. The most common cause of TOA is ascending pelvic inflammatory disease (PID) or any upper genital tract infection (Beigi 2015a). Prior to the use of antibiotics and current surgical techniques, the mortality rate as a result of TOA was over 50% (Sandesh et al. 2014). Currently, the mortality rates are less than 5% for both ruptured and non-ruptured abscesses (Sandesh et al. 2014). Most women with TOA are of reproductive age, and the risk factors are the same as those for PID. These include a prior history of PID, multiple sexual partners, and age between 15 and 25 years. In addition, patients undergoing oocyte retrieval during ART are at an increased risk of developing TOAs (McNeely et al. 1998).

The microbiology of PID is complex and often includes both aerobic and anaerobic organisms such as *E. coli*, aerobic streptococci, such as *S. agalactiae*, and *Bacteroides fragilis*. Although TOAs are often associated with microorganisms similar to those found in PID, *Neisseria gonorrhea* and *Chlamydia trachomatis* are not often seen in cases of TOA (Beigi 2015a).

Patients with TOA often present with a similar clinical presentation as those with PID. Symptoms include lower abdominal pain, fever, chills, and vaginal discharge. Patients with a ruptured TOA are more likely to present with signs and symptoms of acute abdomen or sepsis (Beigi 2015a). On physical examination patients with PID or TOA may present with vaginal discharge, cervical motion tenderness, fevers, tachycardia, rebound tenderness and guarding on abdominal exam, as well as vaginal discharge. Workup of a patient with suspected PID/TOA should include a complete blood count (CBC), erythrocyte

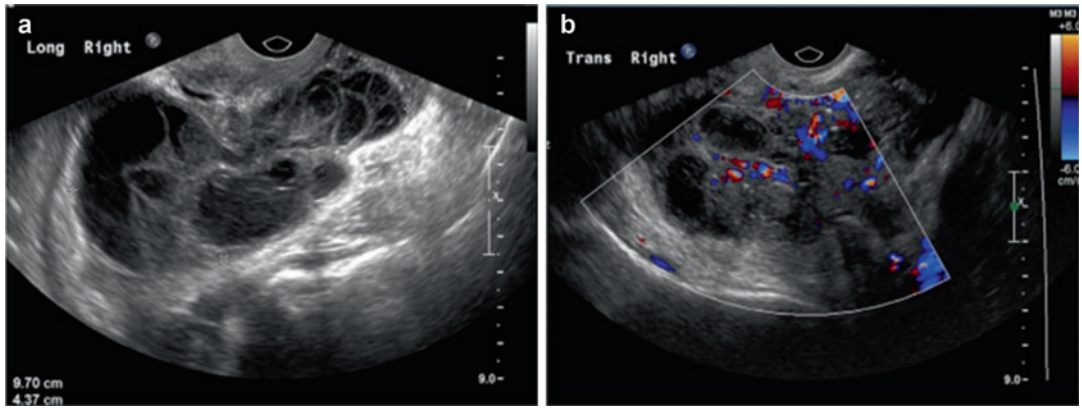

Fig. 4 **a**, **b** A 47-year-old female with complex and solid cystic mass in the right adnexa with internal vascularity in this patient with tubo-ovarian mass. Patient underwent percutaneous transgluteal drainage under CT guidance (Swenson et al. 2014)

sedimentation rate (ESR) or C-reactive protein (CRP), a pregnancy test, as well as nucleic acid amplification testing (NAAT) for *N. gonorrhea* and *C. trachomatis* (Sandesh et al. 2014). Abnormalities seen in these tests include elevated white blood cell count, ESR, and CRP levels.

Rapid and accurate diagnosis of TOA is crucial since delaying treatment can lead to further sequelae such as infertility, future ectopic pregnancy, and chronic pelvic pain (Beigi 2015a). Imaging is indicated in patients with PID who are acutely ill or have severe abdominal tenderness, as well as when there is suspicion for a TOA. Ultrasound is the imaging modality of choice due to accuracy and cost efficiency. On ultrasound, TOAs appear as complex multilocular masses that often alter the normal architecture of the adnexa as seen in Fig. 4. They tend to have internal echoes that are consistent with inflammatory debris (Dupuis and Kim 2015). CT scan has increased sensitivity and may exclude other abdominal pathologies; however, the financial cost to the hospital is much greater. Findings on CT scan include thick-walled, rim-enhancing adnexal masses, with high-density fluid indicative of pus (McNeely et al. 1998).

Management of TOA can be medical or surgical, based on the severity of the clinical presentation and the qualities of the abscess on imaging. Antibiotic therapy is sufficient in 70% of patients with TOA (Tan et al. 2014).

> Candidates for antibiotics are those who are hemodynamically stable without signs of rupture and have an abscess less than 9 cm and who show an initial adequate response to antibiotic therapy (Beigi 2015b).

Patients undergoing medical treatment will often show signs of improvement within 48–72 h of treatment (Beigi 2015b). Those who do not improve within this time period or worsen will require either drainage or surgery. Table 1 outlines the various inpatient and outpatient regimens for treatment of TOA, but triple therapy with ampicillin, gentamicin, and clindamycin has been shown to be superior to the standard regimen of cefoxitin or cefotetan, plus doxycycline (Beigi 2015b). The first 48–72 h period of antibiotics treatment is critical, as there is high risk of rupture and sepsis. There are no determined guidelines for the duration of antibiotic therapy; however, the most commonly reported is 10–14 days (Beigi 2015b).

Surgical management is necessary when rupture is suspected, and antibiotic therapy should be initiated immediately even when surgical management is chosen. Laparotomy is the approach of choice for most physicians due to improved visibility of the entire pelvis; however, a minimally invasive approach has been employed successfully in patients without evidence of rupture

Table 1 Antibiotic regimens for inpatient and outpatient treatment of tubo-ovarian abscess

Regimen	Dose
Inpatient treatment	
Cefoxitin and	2 g IV every 6 h
Doxycycline	100 mg PO or IV every 12 h
Cefotetan and	2 g IV every 6 h
Doxycycline	100 mg PO or IV every 12 h
Clindamycin and	900 mg IV every 8 h
Gentamicin	2 mg/kg loading dose ➔ 1.5 mg/kg every 8 h IV/IM
Ampicillin and	2 g IV every 6 h
Clindamycin and	900 mg IV every 8 h
Gentamicin	2 mg/kg loading dose ➔ 1.5 mg/kg every 8 h IV/IM
Outpatient treatment	
Levofloxacin and	500 mg PO daily
Metronidazole	500 mg PO twice daily

Beigi (2015b)

and is generally performed by experienced surgeons (Beigi 2015b). A minimally invasive laparoscopic approach has been shown to have low complication rates when offered to patients who desire to preserve fertility (McNeely et al. 1998). Intraoperatively, excision of the abscess is carefully performed followed by copious irrigation of the peritoneal cavity to decrease the intensity of inflammation. A positive response is seen in 90–100% of patients who undergo immediate surgical treatment with laparoscopy, while 20–87% of patients undergoing medical management will show a positive response (Beigi 2015b).

Ultrasound- or CT-guided drainage of the TOA is another treatment option that is widely used. It has been shown that abscess drainage with antibiotic therapy has a higher rate of successful treatment when compared to antibiotics alone (McNeely et al. 1998). Image-guided TOA drainage secondary to PID has been shown to help avoid subsequent salpingo-oophorectomy in 94% of patients (McNeely et al. 1998).

6 Ruptured Ovarian Cysts

Ruptured ovarian cysts can lead to gynecologic emergencies. When an ovarian cyst ruptures, the patient may be asymptomatic, or she can have sudden onset abdominal pain as is seen in the pathologies reviewed above. Upon evaluation of the patient, it is important to determine the risks for cyst rupture. These include ovarian cysts, endometriosis, PID, and coagulation abnormalities.

On physical exam, the patient is usually hemodynamically stable, although she can present with a low-grade fever. Right lower-quadrant pain on palpation is most often seen as the sigmoid colon can have a protective effect over the left ovary (Seeber and Barnhart 2006). Some patients may present with signs of acute abdomen if sebaceous material or blood leaks into the abdomen. Blood may also leak into the ovary, which can cause the patient pain due to stretching of the ovarian cortex (Seeber and Barnhart 2006).

Laboratory and imaging studies for these patients is similar to those performed in the pathologies mentioned previously.

- As with any gynecologic workup, pregnancy must first be ruled out.
- However, if the patient is pregnant, ectopic pregnancy must also be ruled out. In addition to hCG, CBC, urinalysis (UA), blood, and urine cultures should be obtained to determine if there is an infectious cause.
- Ultrasound is also preferred in the evaluation of ruptured ovarian cyst for the same reasons of cost efficiency and diagnostic accuracy. On US, an adnexal mass and fluid in the pelvis will be seen as in Fig. 5 (Swenson et al. 2014). Of note, these findings can be similar to those found with ectopic pregnancy or pus from a TOA. If diagnosis is still unclear after US, CT may be performed due to improved visualization of the ovary.

Management of ruptured ovarian cysts is dictated by whether the cyst is complex or simple and whether the rupture is complicated or not. Ovarian

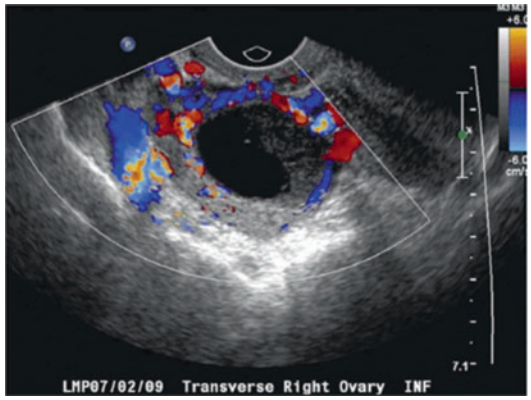

Fig. 5 Complex cystic structure in the right ovary with heterogeneous internal echoes and peripheral solid components with a peripheral ring of vascularity, consistent with a hemorrhagic corpus luteum cyst (Swenson et al. 2014)

cyst rupture is classified as uncomplicated when the patient is hemodynamically stable without signs of acute abdomen or an expanding hemoperitoneum. Such patients may be treated on an outpatient basis with oral analgesia, allowing for the cyst fluid to be resorbed spontaneously within 24–48 h, with subsequent improvement of symptoms (Seeber and Barnhart 2006). If the cyst rupture is complicated by large and ongoing blood loss, then patients are usually hospitalized for serial monitoring of vital signs, abdominal exams, and monitoring of hemoglobin and hematocrit levels to determine whether or not further intervention is required (Seeber and Barnhart 2006). Surgical intervention is recommended when bleeding is ongoing or if there are signs of hemodynamic instability. Choosing an exploratory laparotomy or a minimally invasive laparoscopic approach depends on the hemodynamic stability of the patient and the expertise of the surgeon. In most cases laparoscopic ovarian cystectomy with control of bleeding is feasible and is the preferred method in premenopausal patients. An oophorectomy is an acceptable option for postmenopausal patients (Herman et al. 2015).

7 Conclusion

Acute pelvic pain is common presenting complaint that could result from various pathologies. It is critical for clinicians to be able to combine clinical judgment with imaging and laboratory findings in order to make an accurate diagnosis and properly treat the patient. Prompt appropriate treatment is of utmost importance as the consequences of misdiagnosis or mistreatment can be devastating.

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Diagnosis and Treatment of Premenstrual Syndrome

Differentiating PMS from Premenstrual Dysphoric Disorder PMDD and Premenstrual Exacerbation Disorder PMED

Donna Shoupe

Contents

Abstract

Controversy has always surrounded premenstrual syndrome (PMS). The varying attitudes toward women with PMS symptoms have ranged from "it's all in your head" to "your hormones are controlling you." In the 1870s, Dr. Clarke published a book entitled *Sex in Education or A Fair Chance for the Girls* arguing that women who had sustained vigorous mental activities or who studied in a "boy's way" risked atrophy of the ovaries and uterus, sterility, insanity, masculinization, insanity, or even death. He argued that young women should study no more than 4 h per day and should not study during their menses. It took many decades of social and scientific evidence to silence these arguments. An ongoing controversy around PMS in the twenty-first century surrounds the various explanations as to how and why women respond so differently to the ups and downs of ovarian hormones during the menstrual cycle. The relatively recent separation of premenstrual syndrome (PMS) from premenstrual dysphoric disorder (PMDD) and premenstrual exacerbation disorder (PMED) has led to significant progress for a better understanding of PMS and development of more effective and safer treatment regimens.

Keywords

Premenstrual syndrome • Premenstrual dysphoric disorder • Premenstrual exacerbation disorder • Serotonin • Ovarian hormones and

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mood disorders • Suppression of ovulation • SSRI • DSM-5 • Mood disorders • Luteal phase symptoms • Luteal phase disorder • PMS • PMS diary • PMDD • Anxiety • Depression • Molimina

1 Introduction

It is important for clinicians to understand that PMS and PMDD are now considered two separate diagnoses holding distinct ICD-10 codes (Gynecology diagnosis N94.3 versus Psychiatry diagnosis F38.8). These two entities, although related in part, have separate diagnostic criteria and management guidelines. There is also recognition of an emerging disorder named premenstrual exacerbation (PME) that refers to a condition where follicular phase mood disorder symptoms worsen during the luteal phase (Biggs and Demuth 2011) (Halbreich 2004). Of note, women with PMDD have a high lifetime incidence (up to 50–78%) of various Axis 1 disorders including bipolar depression, generalized anxiety disorders, and major depressive disorders that may complicate the diagnosis and treatment options (Rapkin and Lewis 2013).

2 Diagnosis Criteria

The percentage of reproductive-aged women with premenstrual molimina (breast pain, bloating, constipation, acne) is reported as high as 80–90% (Halbreich 2004). Importantly, these symptoms are not severe and do not impact lifestyles. The most simple and straightforward diagnosis of PMS relies on a consistent pattern of moderate emotional symptoms often coupled with various physical symptoms occurring only during the luteal phase that are strong enough to disrupt normal life. Possible symptoms are listed in Table 1.

As emphasized above, the symptoms associated with the diagnosis of PMS are not present during the follicular phase. These symptoms also disappear during pregnancy, OCP use, and menopause. Alternatively, if symptoms are severe and significantly impair daily lives and personal relationships, the correct diagnosis is now considered to be PMDD. An additional consideration is that exacerbation of symptoms during the luteal phase that are also present during the follicular phase is premenstrual exacerbation and not PMS or PMDD.

Table 1 Common emotional and physical symptoms associated with of PMS

Emotional symptoms	Physical symptoms
Moodiness/mood swings	Swollen/edematous
Sadness	Body aches
Anxiety	Breast tenderness
Irritability	Headaches
Poor impulse control	Weight gain
Insomnia/hypersomnia	Tiredness
Withdrawal from usual activities	Skin disorders (acne)
Decreased concentration	Insomnia
Nervousness	Lethargy

3 Epidemiology

Although estimates vary, the general consensus is that PMS occurs in up to 30–40% of reproductive-aged women. PMDD, a severe and disabling condition whose diagnosis is listed under a psychiatric ICD-10 code, affects 3–8% of women of the PMS population (that is, in the population of women with luteal phase emotional symptoms) (Halbreich 2004) (Endicott et al. 2003).

Diagnosis

The diagnosis of PMS requires:

1. Moderate emotional symptoms (Table 1) that impact lifestyle that appear repeatedly during the luteal phase and disappear within a few days of the beginning of menses, preferably documented prospectively by a daily diary for at least 2 months.

According to the American College of Obstetricians and Gynecologists criteria for the diagnosis of PMS, symptoms of PMS should be relieved within 4 days of menses onset and do not occur until at least menstrual day 13, excluding women

Table 2 Diagnostic criteria for PMDD according to the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V abbreviated)

Criterion A – in most menstrual cycles, at least five of these symptoms	Marked irritability or anger
	Marked lability (mood swings)
	Marked anxiety and tension
	Marked depressed mood
	Decreased interest in usual activities
	Marked changes in appetite
	Lethargy, marked lack of energy
	Hypersomnia or insomnia
	Feeling overwhelmed/out of control
	Physical symptoms (breast swelling and tenderness, joint or muscle pain, bloating, or perceived weight gain)
Criterion B – one or more must be present	Marked irritability or anger or increased interpersonal conflicts
	Marked affective lability (marked mood swings, increased sensitivity to rejection)
	Marked depressed mood, feelings of hopelessness, or self-deprecating thinking
	Marked anxiety, tension, "keyed up or on edge"
Criterion C – one or more must be present	Decreased interest in usual activities
	Lethargy, marked lack of energy, easy fatigability
	Marked change in appetite; overeating or specific food craving
	Sense of being out of control or overwhelmed
	Hypersomnia or insomnia
	Physical symptoms (as in A)

with any hormone intake, pharmacological treatment, alcohol drinking, or socioeconomic performance disability (ACOG 2000). Certain laboratory tests may exclude thyroid dysfunction, anemia, or electrolyte disturbances. Exclusion of symptoms associated with medical problems such as migraines, epilepsy, asthma, diabetes, allergies, autoimmune disorders, and irritable bowel syndrome is important, as changes in ovarian hormones may affect symptoms associated with these disorders (Halbreich et al. 2006).

There are many available diaries (Daily Record of Severity of Problems (DRSP)) that are most commonly used in research studies on PMS. Patients may download any of a host of free PMS diaries from online sources or one of the many available apps. Most clinicians often make decisions on diagnosis and treatments that are based on retrospective patient histories. Listing of particular emotional and physical symptoms can help to direct treatment selections.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), to make the diagnosis of PMDD, it is necessary to meet the three criteria as listed in Table 2. The symptoms must be present in the final week before the onset of menses, start to improve within a few days of menses, and be minimal or absent in the week post-menses (Diagnostic 2006).

4 Etiology

The etiology of PMS is not fully understood, but the onset of symptoms is associated with ovarian sex hormones. Women with PMS have exaggerated responses to these hormones and generally find relief with modulation of these hormones. Studies often implicate serotonin as the CNS neurotransmitter that links ovarian sex hormones to adverse emotional effects, particularly depression (Hantsoo and Epperson 2015). It is in the patients with PMDD, however, that the data linking

estrogen, serotonin, and adverse emotional symptoms have been most convincing (Rapkin 2012).

Treatment

Because the etiology of PMS remains unknown, the treatment options are individualized and directed at symptom relief.

The primary treatment option for women with PMS is combined contraceptive pills (COCP). COCPs provide contraceptive protection; decrease molimina symptoms, bleeding issues, and dysmenorrhea; and importantly suppress ovulation and the ups and downs of ovarian hormones. The COCP containing drospirenone plus ethinyl estradiol has an FDA approval for PMS although most other pills also have effectiveness.

Although use of cyclic luteal phase or continuous administration of serotonergic antidepressants (SSRIs) can effectively improve mood and depressive symptoms in PMS patients (Marjoribanks et al. 2013) (Cunningham et al. 2009) (Dimmock et al. 2000) (Shah et al. 2008), this treatment tends to be the first-line treatment option in women with PMDD(Cunningham et al. 2009) and a second-line treatment in PMS. Side effects of SSRIs are common and dose-dependent and include decreased libido, sweating, nausea, decreased energy, withdrawal symptoms, and fatigue. A trial of SSRI therapy starting with continuous use is reasonable. If a positive response is seen, switching to a luteal phase-only treatment regimen is a practical, cost-effective option. All SSRIs are rated pregnancy category C (risk not ruled out; drug should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus) with the exception of paroxetine that is listed as pregnancy category D (due to possible increased risk of cardiac defects primarily atrial and ventricular septal defects). Side effects commonly reported with use of SSRIs include dry mouth, agitation, dizziness, anxiety, somnolence, and constipation.

Other options to suppress ovulation include GnRH agonists (with and without add back), Depo-Provera, and Mirena IUD. Their selection is based on individual patient symptom profiles. Other psychotropic agents are low-dose clomipramine (a tricyclic antidepressant; pregnancy category C) or benzodiazepines (particularly useful in patients with irritability), although their efficacy is somewhat reduced compared to SSRIs and they are listed as pregnancy category D (there is positive evidence of human fetal risk, but the potential benefits may warrant the use of the drug in pregnant women despite potential risks) (Nevatte et al. 2013). Studies using spironolactone (pregnancy category C) or other diuretics have demonstrated mixed results.

Other non-pharmacological treatment modalities include lifestyle modifications, cognitive behavior therapy, and herbal options (Table 3). Journals and textbooks are filled with a variety of papers (with mixed findings) or

Table 3 Non-pharmacological treatment recommendations for PMS

Lifestyle modifications	Regular aerobic exercise (Vishnupriya and Rajarajeswaram 2011), deep breathing exercises to reduce anxiety, yoga or massage to relieve stress
	Avoiding stress
	Adjust sleeping habits to get plenty of sleep
	Increase in complex carbohydrates (increases tryptophan, a precursor to serotonin) (Sayegh et al. 1995); limit salty foods; in small portions, eat smaller meals to reduce bloating
Cognitive behavior therapy	Therapy designed to correct problematic, disruptive thoughts, emotions, and behaviors (Lustyk et al. 2009)
	Designed to decrease nervousness, addictive behavior, and pain
Dietary supplementation (mixed results)	Calcium carbonate 1200 mg/day (Thys-Jacobs et al. 1998)
	Vitamin B6 80 mg/day (Kashanian et al. 2007)
	Pyridoxine > 300 mg/day

nonscientifically established recommendations on the effects on PMS symptoms associated with modulations in calcium, vitamin D, vitamin E, vitamin B6, caffeine, salt, alcohol, carbohydrates, fish, spousal support, curcumin, sleep quality, St John's wort, chaste tree extract (chasteberry), ginkgo biloba, *Justicia pectoralis*, primrose oil, saffron, myo-inositol, western diet, stress, STDs, athletic activity, yoga, and illicit drugs. Individuals may or may not find relief with these treatments, and further trials are encouraged (Table 3).

5 Conclusions

Accurate confirmation of a lack of follicular phase symptoms and the presence of recurrent luteal phase symptoms is important to establish a diagnosis of PMS. The first-line treatment option for PMS is suppression of ovulation through the use of oral contraceptive pills or other treatment options that suppress ovulation or interrupt the patient's cyclic ovarian hormone pattern (Ryu and Him 2015). Cyclic or continuous treatment with SSRIs is primarily reserved for women with the more severe anxiety or irritability symptoms associated with PMDD. Generally, treatments are directed at alleviating individual symptoms. Non-pharmacological treatments and lifestyle interventions may be beneficial, but results are inconsistent.

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Management of Early-Stage and Locally Advanced Cervical Cancer

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Contents

Abstract

Carcinoma of the cervix remains a significant health problem for women worldwide. However, the use of a multidisciplinary approach to the treatment of cervical cancer has led to a marked improvement in patient outcomes. It has been demonstrated that early-stage cervical cancer can be effectively treated with radical surgery or definitive radiotherapy, which achieve similar survival outcomes. To reduce the frequency of postoperative complications, less invasive surgical procedures involving laparoscopic or robotic approaches have been introduced. Moreover, for patients who wish to preserve their fertility, fertility-preserving surgery has been developed. Concurrent chemoradiotherapy with a platinum-based agent is the recommended treatment for locally advanced cervical cancer. The standard concurrent chemotherapy regimen involves the administration of single-agent cisplatin at a weekly dose of 40 mg/m^2 during external beam radiotherapy. Overall, when added to radiotherapy, cisplatin was demonstrated to reduce the risk of death from cervical cancer; i.e., it resulted in an absolute overall survival benefit of 10 %. In this chapter, we summarize the current management strategies for early and locally advanced cervical carcinoma.

Keywords

Cervical cancer • Surgery • Neoadjuvant chemotherapy • Radiotherapy • Prognostic factors

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1 Introduction

Currently, early-stage cervical cancer can be effectively treated with radical surgery or definitive radiotherapy, which achieves similar survival outcomes. Concurrent chemoradiotherapy (CCRT) with a platinum-based agent is the recommended treatment for locally advanced cervical cancer. In this chapter, we summarize the findings of important clinical studies conducted in the past few decades and review the current standard management strategies for early-stage and locally advanced cervical carcinoma.

1.1 Early-Stage Cervical Cancer

1.1.1 Stage IA

Historically, it was considered that FIGO stage IA1 or 1A2 adenocarcinoma of the cervix behaves more aggressively than FIGO stage IA1 or 1A2 squamous cell carcinoma. However, recent studies have demonstrated that the prognosis of FIGO stage IA1 or 1A2 adenocarcinoma of the cervix is comparable to that of squamous cell carcinoma of the cervix (Hirai et al. 2003; Ceballos et al. 2006).

Stage IA1

It has been reported that the risk of lymph node metastasis is generally very low (Table 1) in patients with stage IA1 cervical cancer (Elliott et al. 2000; Hirai et al. 2003; Kasamatsu et al. 2002; Lee et al. 2006). Moreover, as no parametrial involvement is observed in patients with stage IA1 cervical cancer (Hirai et al. 2003; Kasamatsu et al. 2002; Reynolds et al. 2010), the recommended treatment for such disease is extrafascial hysterectomy. However, a previous report found that 8.2 % of patients that exhibited lymphovascular space invasion (LVSI) developed lymph node metastases, compared with 0.8 % of the patients without LVSI (Benedet and Anderson 1996). Thus, in cases in which the patient's conization specimen demonstrates extensive LVSI, a more radical approach involving a modified radical hysterectomy (RH) and pelvic lymphadenectomy is recommended. Observation might be an appropriate option for patients that exhibit negative margins and LVSI after cone biopsies and wish to preserve their fertility (Wright et al. 2010).

Stage IA2

According to previous studies, the risk of parametrial involvement is very low (∼1 %) in patients with stage IA2 cervical cancer (Table 2). As there is potential for lymph node metastasis to develop in patients with stage IA2 disease (Buckley et al. 1996; Lee et al. 2006; Poynor et al. 2006; van Meurs et al. 2009), the recommended treatment for stage IA2 cervical cancer is modified RH and pelvic lymphadenectomy. However, medically unfit patients can be treated with definitive radiotherapy consisting of pelvic external beam radiotherapy and brachytherapy. On the other hand, a combination of radical trachelectomy and pelvic lymphadenectomy is recommended for patients who wish to preserve their fertility.

1.1.2 Stage IB1–IIA

Surgery and Radiotherapy

FIGO stage IB1–IIA cervical cancer can be effectively treated with surgery or radiotherapy, which achieves similar survival outcomes. As pelvic node metastasis is common (frequency:

Table 1 Incidence of lymph node metastasis in patients with FIGO stage IA1 cervical cancer

Author	No. Patients	Nodal metastasis (%)
Hirai Y 2003	22	0 (0)
Kasamatsu T 2002	21	0 (0)
Lee KB 2006	174	1 (0.6)
Elliott P 2006	121	1 (0.8)

Table 2 Incidence of lymph node metastasis in patients with FIGO stage IA2 cervical cancer

Author	No. Patients	Nodal metastasis (%)
Buckley SL 1995	94	7 (7.4)
Lee KB 2006	28	1 (3.7)
Poynor EA 2006	12	0 (0)
van Meurs H 2009	48	0 (0)

>10 %) in this patient population, the standard surgical management strategy is RH and bilateral pelvic lymph node dissection. For patients with stage IB1 disease who wish to preserve their fertility, radical trachelectomy combined with pelvic lymphadenectomy is an option, especially for those with tumors measuring ≤2 cm in diameter.

According to previous reports including a prospective randomized study, the 5-year survival rate of FIGO stage IB–IIA cervical cancer patients that are treated with radical surgery ranges from 83 % to 91 %, which is comparable to the 74–91 % 5-year survival rate reported for those treated with radiotherapy alone (Landoni et al. 1997; Perez et al. 1987).

Neoadjuvant Chemotherapy Before Radical Surgery

Clinical trials of neoadjuvant chemotherapy (NACT) have been conducted in order to improve the prognosis of surgically treated cervical cancer patients; however, they obtained conflicting results (Rydzewska et al. 2012). The clinical benefit of NACT has recently been addressed in a meta-analysis of six phase III trials comparing NACT plus surgery with surgery alone (Rydzewska et al. 2012). The NACT regimens varied between the trials, but NACT achieved favorable clinical response rates ranging from 52 % to 84 %. The addition of NACT was associated with significantly improved local recurrence (odds ratio, 0.67; 95 % confidence interval (CI), 0.45 to 0.99, $P = 0.04$), overall survival (OS) (hazard ratio (HR), 0.77; 95 % CI, 0.62 to 0.96, $P = 0.02$), and progression-free survival (PFS) rates (HR, 0.75; 95 % CI, 0.61 to 0.93, $P = 0.008$). However, only three of the trials included in this meta-analysis demonstrated a statistically significant benefit of NACT in terms of OS, whereas others found that NACT was of no benefit (Rydzewska et al. 2012). Thus, further studies involving the current standard chemotherapy (i.e., paclitaxel combined with cisplatin or carboplatin) should be conducted in the future to draw definitive conclusions regarding the benefits of NACT.

Risk Factors for Recurrence

A number of pathological risk factors that compromise the treatment outcomes of cervical cancer patients that are primarily treated with RH have been identified (Delgado et al. 1990; Fuller et al. 1989). For example, patients with positive pelvic lymph nodes, parametrial invasion, or positive surgical margins are regarded as being at high risk of recurrence. Moreover, patients with tumors that are confined to the cervix and display risk factors for recurrence, such as a large tumor (≥4 cm), LVSI, or deep stromal invasion, are considered to be at intermediate risk of recurrence (Delgado et al. 1990; Fuller et al. 1989).

Among these prognostic factors, nodal metastasis remains the single most important prognostic factor in cervical cancer. It has been reported that pelvic lymph node metastasis is associated with a 30–50 % reduction in the 5-year survival rate, and the survival of patients with positive pelvic lymph nodes is further affected by the number of positive pelvic lymph nodes (Delgado et al. 1990; Fuller et al. 1989). In addition, previous studies have found that the survival time of early-stage cervical cancer patients with ≥3 positive lymph nodes was significantly shorter than that of patients with 1 or 2 positive lymph nodes (Kamura et al. 1992; Okazawa et al. 2012).

In addition to the six risk factors mentioned above, the histological subtype of early-stage cervical cancer might also impact on survival. Previous case series have consistently suggested that small cell carcinoma has an unequivocally poor prognosis (Kuji et al. 2013; van Nagell et al. 1988). Some previous retrospective studies have found that patients with adenocarcinoma have a worse prognosis than those with squamous cell carcinoma, whereas others did not detect any survival differences between the two subtypes (Mabuchi et al. 2012a; Park et al. 2010). The prognostic significance of adenosquamous carcinoma is also disputed: some authors have reported that patients with adenosquamous carcinoma have comparable survival outcomes to those with adenocarcinoma, but have a worse prognosis than those with squamous cell carcinoma, whereas others have not detected any difference in survival between adenosquamous carcinoma and

squamous cell carcinoma (Baek et al. 2014; Mabuchi et al. 2012b).

Tailored Postoperative Adjuvant Radiotherapy Based on Pathological Risk Assessments

For patients that exhibit intermediate-risk or high-risk prognostic factors, the administration of adjuvant external beam radiotherapy to the whole pelvis has been recommended as a way of reducing the risk of recurrence. In such regimens, the total radiation dose administered during the external beam radiotherapy has been reported to range from 46 to 50.4 Gy.

A Gynecologic Oncology Group phase III study (GOG 109/SWOG 8797) demonstrated that the addition of cisplatin-based concurrent chemotherapy to postoperative radiotherapy improved both PFS and OS in patients with high-risk factors (Peters et al. 2000).

As for patients with intermediate-risk factors, a GOG phase III study (GOG 92) found that adjuvant radiotherapy alone significantly reduced the risk of recurrence and prolonged PFS (Rotman et al. 2006). Although several retrospective studies have suggested that adjuvant CCRT produces superior outcomes to pelvic radiotherapy in patients with intermediate-risk factors, so far, the advantages of postoperative CCRT over radiotherapy alone in this patient population have never been demonstrated in a randomized prospective trial (Kim et al. 2009; Okazawa et al. 2013).

Minimally Invasive Approaches

Laparoscopic and Robotic Surgery

Minimally invasive surgery, including traditional laparoscopy and robotic-assisted laparoscopy, is being used increasingly and frequently in the surgical management of gynecological malignancies.

Laparoscopic RH (LRH) has been used for the management of uterine cervical cancer since the early 1990s. As for robotic RH (RRH), the Food and Drug Administration approved the use of this approach during gynecological surgery in 2005. Retrospective studies have shown that LRH and RRH are safe, feasible, and associated with less blood loss, fewer postoperative complications, and a shorter hospital stay than standard abdominal RH (ARH) in patients with cervical cancer (Nam et al. 2012). However, the feasibility and efficacy of LRH and RRH have not been demonstrated in the prospective setting.

In a recent meta-analysis evaluating the outcomes of LRH, RRH, and ARH, all three types of RH resulted in similar recurrence rates (Geetha and Nair 2012). The number of lymph nodes dissected and the frequencies of nodal metastasis and positive margins were also similar in all three types of RH. However, ARH was associated with significantly greater blood loss and a significantly higher transfusion rate than both LRH and RRH. Postoperative infections were significantly more common among the patients who underwent ARH than among those that underwent the other two methods. In addition, the patients that underwent RRH stayed in hospital for significantly shorter periods than those treated with the other two methods. Although the long-term oncological outcomes of the LRH or RRH have not been fully investigated, the abovementioned results indicate that minimally invasive laparoscopic or robotic surgical procedures are appropriate options for radical surgery for early-stage cervical cancer.

Currently, a prospective randomized trial is underway to compare the roles of ARH, LRH, and RRH in the management of early-stage cervical cancer (Obermair et al. 2008).

Less Radical Surgery

As RH frequently results in serious complications, it is important to identify patients whose lesions are amenable to less radical surgery.

In 2012, the results of a randomized study comparing RH versus simple hysterectomy plus the removal of the upper one third of the vagina (SH) in patients with FIGO stage IB1 or IIA1 ($\leq$4 cm) cervical cancer were reported (Landoni et al. 2001). Sixty-two patients were randomized to undergo a SH, while 63 patients were randomized to the RH group. Adjuvant radiotherapy was given to the patients that exhibited positive or close ($<$3 mm) surgical margins, LVSI close to the resection margin, or lymph node metastases. No significant differences in the recurrence rate or

OS were observed between the two arms (Landoni et al. 2001, 2012). However, SH was found to be significantly superior to RH in terms of urological morbidities. When analyzed according to tumor size, the survival of patients with tumors measuring $\leq$3 cm did not differ significantly between the two groups (15-year OS, 76 % vs. 80 %, $p = 0.88$); however, in the patients with tumors measuring between 3.1 cm and 4 cm in diameter, radical surgery was associated with a significant improvement in survival (15-year OS, 74 % vs. 97 %, $p = 0.03$). The results of this trial suggest that the surgical removal of the parametrium might not be necessary in some women with small cervical tumors and good prognostic factors.

Previous studies have tried to identify predictors of parametrial tumor spread and subsets of patients that are at low risk of parametrial disease. In one of these studies, it was noted that negative pelvic nodes, the absence of LVSI, and tumors that measure $<$2 cm in diameter are associated with a low risk of parametrial disease, i.e., an incidence of less than 1 % (Kato et al. 2015). Of these, a tumor diameter of $<$2 cm was the most consistently reported factor in similar studies. In a recent large retrospective study, it was suggested that parametrial involvement was present in 1.9 % (6/323) of tumors measuring $\leq$2 cm in diameter (Kato et al. 2015). These results indicate that less radical surgery might be a reasonable treatment option for early cervical carcinoma, especially for tumors measuring $\leq$2 cm in diameter.

Sentinel Lymph Node Biopsy

In early-stage cervical cancer patients, sentinel lymph node biopsy has been utilized to reduce the risk of postoperative complications after lymph node dissection and to precisely predict the status of regional lymph node metastasis. Two types of tracer are commonly available for the detection of sentinel lymph nodes: radioactive isotopes and vital dyes (Lécuru et al. 2011). A meta-analysis of 67 studies reported that the pooled detection rate of sentinel lymph nodes was 90.9, 80.9, and 92.3 % when radioactive isotopes, vital dyes, and a combination of the two types of tracer were used, respectively (Kadkhodayan et al. 2015). Sentinel lymph node biopsy appears to be more accurate at determining lymph node status than commonly used imaging techniques, such as positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT). This was illustrated in a meta-analysis of 72 studies, involving 5,042 women with cervical cancer, that evaluated several approaches and found that the sensitivity and specificity of sentinel lymph node biopsy for detecting lymph node metastases were as high as 91 % and 100 %, respectively, whereas the sensitivity and specificity values of the abovementioned imaging methods were as follows: PET, 75 % and 98 %, respectively; MRI, 56 % and 93 %, respectively; and CT, 58 % and 92 %, respectively (Selman et al. 2008). Further studies are required before sentinel lymph node mapping is routinely employed during the treatment of early-stage cervical cancer.

2 Locally Advanced Disease (IIB–IVA)

2.1 Primary Surgical Approach for FIGO Stage IIB Disease

The standard treatment for FIGO stage IIB–IVA cervical cancer is definitive pelvic radiotherapy. However, some European and Japanese institutions have treated stage IIB disease with radical surgery (Kasamatsu et al. 2009; Mabuchi et al. 2011). Retrospective studies of patients with FIGO stage IIB disease have suggested that patients that are treated with radical surgery and those that are treated with definitive radiotherapy exhibit similar treatment outcomes (estimated 5-year survival rates of 64–69 %) (Kasamatsu et al. 2009; Mabuchi et al. 2011).

2.2 Radiotherapy

In patients with locally advanced cervical cancer who were free from para-aortic lymph node metastases, an earlier randomized trial conducted by the Radiation Therapy Oncology Group

(RTOG 79–20) demonstrated an improvement in survival when prophylactic para-aortic radiotherapy was added to pelvic radiotherapy (Rotman et al. 1995). In a subsequent randomized trial (RTOG 90–01), it was found that pelvic CCRT improved OS and PFS compared with extended field radiotherapy alone in patients with locally advanced cervical cancer (Eifel et al. 2004). In the late 1990s, four other studies evaluated the survival benefit of adding concurrent chemotherapy to standard definitive radiotherapy (Keys et al. 1999; Morris et al. 1999; Rose et al. 1999; Whitney et al. 1999). Overall, when added to radiotherapy, cisplatin was demonstrated to reduce the risk of death from cervical cancer, with an absolute OS benefit of 10 % (Keys et al. 1999; Morris et al. 1999; Rose et al. 1999; Whitney et al. 1999). Based on these findings, it is recommended that patients with stage IB2 or more advanced cervical cancer should receive platinum-based pelvic CCRT, except in cases where there are medical contraindications. The standard CCRT regimen involves the administration of single-agent cisplatin at a weekly dose of 40 mg/m^2 during external beam radiotherapy.

2.3 Prognostic Factors for Survival

Despite the overall improvement in patients' prognosis, the efficacy of the standard CCRT regimen is far from optimal in patients with locally advanced cervical cancer. According to an updated report from the RTOG (protocol 90–01), the 5-year survival rate of patients with stages IB–IIA that are treated with a combination of chemotherapy and radiotherapy is 78 %, whereas the equivalent rate for patients with stages III–IVA disease is 59 % (Eifel et al. 2004). In addition to an advanced clinical stage, larger tumors, nodal involvement, pretreatment hemoglobin levels of $<$12.0 mg/ml, pretreatment leukocytosis, an overall treatment time of $>$56 days, and adenocarcinoma histology have been identified as independent risk factors that compromise the treatment outcomes of radiotherapy (Grigiene et al. 2007; Serkies et al. 2006; Mabuchi et al. 2014; Perez et al. 1995; Rose et al. 2014).

3 Follow-up After Primary Treatment

The concept of posttreatment follow-up is based on the premise that early detection before the development of symptoms will result in decreased morbidity and mortality rates. As the follow-up programs employed after the treatment of uterine cervical cancer have never been evaluated in a prospective setting, the most appropriate modalities and the optimal timing of posttreatment follow-up has not been established. However, as roughly 80 % of recurrent lesions are diagnosed in the first 2 years after the initial therapy, careful posttreatment follow-up examinations should be performed frequently during this critical period.

4 Conclusion

Recent advances in surgery and radiotherapy have significantly improved the outcomes of both early-stage and locally advanced cervical cancer. However, a significant number of patients still suffer recurrence after the current standard primary treatments. As prognostic factors for recurrence are identified from analyses of clinical data, clinical studies of novel treatments should be conducted to improve the prognosis of high-risk cervical cancer patients.

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Diagnosis and Management of Nonepithelial Ovarian Cancer

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Abstract

Nonepithelial ovarian cancers represent a small fraction of ovarian cancers. Malignancies in this category include sex cord-stromal tumors (SCST) and ovarian malignant germ cell tumors (OMGCT), and each of these classifications encompasses multiple histologic subtypes. The most common SCST include granulosa cell and Sertoli-Leydig cell tumors. Dysgerminomas, yolk sac tumors, and immature teratomas are the most frequently encountered OMGCT. The prognosis for these tumors is good; however, the survival outcome is dependent on factors such as tumor subtype and stage at diagnosis. Most patients with nonepithelial ovarian cancers present with low stage disease due to symptoms that occur early in the disease process. Surgery is the mainstay of treatment for all nonepithelial ovarian cancers. If desired, fertility sparing surgery is typically an appropriate management option for both SCST and OMGCT. Postoperative adjuvant chemotherapy is dependent on disease type and stage; however, due to the exquisite chemosensitivity of malignant germ cell tumors of the ovary, platinum-based combination chemotherapy is used for almost all cases. The most commonly used initial regimen for both SCST and OMGCT is combination of bleomycin, etoposide, and cisplatin. Surveillance for recurrent disease is mandated for all SCST and OMGCT, even those that present in early stages.

Keywords

Nonepithelial ovarian cancer • Sex cord-stromal tumors • Malignant germ cell tumors of the ovary • Granulosa • Sertoli-Leydig • Fibroma-thecoma • Gynandroblastoma • Dysgerminoma • Yolk sac • Teratoma

1 Introduction

Ovarian cancers are classified by their histological origin, and the majority of ovarian malignancies are of epithelial origin. Primary nonepithelial ovarian cancers most commonly include those originating from germ cells or sex cord-stromal cells, and there are extremely rare instances of alternative histological subtypes such as carcinosarcomas or lipoid cell tumors. Metastases from other primary sites can also be found on the ovaries; the most well-known example of this phenomenon is Krukenberg tumors. Nonepithelial ovarian cancers are relatively rare entities, composing only five to ten percent of all ovarian cancers (Quirk and Natarajan 2005). There are many similarities between different subtypes of nonepithelial ovarian cancer in epidemiologic presentation and treatment pattern; however, each specific type of tumor has individual clinical characteristics that are important to recognize. Nonepithelial ovarian cancers are often caught at an earlier stage than epithelial type because of more noticeable early symptoms; however, overall prognosis remains mainly dependent on histological subtype, tumor grade, and stage at presentation.

2 Sex Cord-Stromal Tumors

2.1 Pathogenesis

Sex cord-stromal tumors (SCSTs) are cancers that originate from the embryonal stromal or mesenchymal elements of the ovary. These matrix cell elements of the ovary are typically capable of producing sex hormones; so, patients with SCST often present with evidence of excessive estrogen or androgen phenotypes. The SCST subtypes consist of granulosa cell tumors, Sertoli-Leydig cell tumors, fibroma-thecoma tumors, steroid cell tumors, sex cord tumor with annular tubules, gynandroblastoma, and otherwise unclassified tumors. Mixed cell type tumors are relatively common. Refer Table 1 for SCST subtype classification. The typical age of presentation varies according to the subtype.

Table 1 World Health Organization histologic classification for sex cord-stromal tumors

WHO histologic classification	Pathology
Granulosa cell tumor	
Adult	Malignant
Juvenile	Malignant
Sertoli cell tumors	Malignant potential
Sertoli-Leydig cell tumors	
Well differentiated	Malignant potential
Intermediate differentiation	Malignant
Poorly differentiated	Malignant
Heterologous elements	Malignant
Leydig cell tumors	Benign
Stromal-Leydig cell tumors	Benign
SCTAT[a] without Peutz-Jaghers syndrome	Malignant
SCTAT[a] with Peutz-Jaghers syndrome	Benign
Gynandroblastoma	Malignant/malignant potential
Thecoma	
Typical	Benign
Luteinized	Malignant potential
Increased mitotic figures	Malignant potential
Fibroma	
Cellular	Malignant potential
Cellular with increased mitotic figures	Malignant potential
Fibrosarcoma	Malignant
Stromal tumor with minor sex cord elements	Benign
Sclerosing stromal tumor	Benign
Signet ring stromal tumor	Benign
Unclassified	Malignant potential
Steroid cell tumors	Malignant
Unclassified SCST[b]	Malignant potential

[a]Sex cord tumor with annular tubules
[b]Sex cord-stromal tumor

2.2 Granulosa Cell Tumors

Granulosa cell tumors (GCT) are the most common type of SCST, comprising approximately 75 % of SCST (Chen et al. 2003). There are two types of granulosa cell tumor: adult type and juvenile type. Demographically, the age at presentation for GCT is bimodal, with over 90 % of juvenile type presenting prior to puberty, while the average age of presentation for adult type is 50 years (Schumer and Cannistra 2003).

2.3 Adult Type GCT

The presentation of a patient with adult type granulosa cell tumor often presents with signs of hyperestrogenization including heavy abnormal uterine bleeding or postmenopausal vaginal bleeding. Notably, due to the excess estrogen exposure encountered with these tumors, there is an increased risk of coincident endometrial hyperplasia, endometrial carcinoma, and breast cancer (Colombo et al. 2007). Endometrial adenocarcinoma is diagnosed in approximately 5–10 % of patients with adult type GCT (Schumer and Cannistra 2003). Additionally, these tumors sometimes present with symptoms of torsion including acute visceral abdomino-pelvic pain and pressure, nausea, and vomiting. Adult GCT expand rapidly and are often 10–15 cm in diameter at the time of presentation; so, patients can also present with symptoms of mass effect including increasing abdominal girth, early satiety, decreasing appetite, nausea, vomiting, and vague abdominal or pelvic pain. It is not uncommon for women with adult type GCT to present with hemoperitoneum after rupture of one of these large vascular masses.

The most important prognostic factor for adult type GCT is stage at diagnosis. Although adult GCT is considered to be malignant, clinical aggressiveness is not defined by mitotic activity or nuclear atypia (Aboud 1997). The majority, 70–90 %, of GCT is unilateral and diagnosed at stage I disease. For FIGO stage I disease, 5-year survival rate is reported to be 75–95 %; however, that decreases to 55–75 % for stage II disease. Stage III/IV disease has poor 5-year survival rates at 20–50 % (Gurumurthy et al. 2014). Long-term recurrence is relatively high for patients with all stages of disease. Approximately 25 % of patients experience a recurrence, with 30 % recurrences occurring greater than 5 years after treatment and 20 % after 10 years (Gurumurthy et al. 2014).

2.4 Juvenile Type GCT

Juvenile granulosa cell tumor also typically presents with the effects of hyperestrogenization. In prepubertal girls, these tumors can present with signs of isosexual precocious pseudo-puberty, including premature breast and pubic hair development and other secondary sexual characteristics. Amenorrhea or menstrual irregularities can present in young women who are closer to the expected chronologic age of puberty. Like adult type GCT, juvenile type can present with mass effect as described above or hemoperitoneum. Additionally, since these tumors potentially present in reproductive age women, they should be considered in the differential diagnosis of an adnexal mass during pregnancy. GCT are especially concerning as rupture during pregnancy can be catastrophic, with one review finding a 10 % rate of rupture with resulting hemoperitoneum requiring emergent intervention during pregnancy (Blake et al. 2014).

Prognosis for juvenile type GCT is also dependent on stage at presentation, and these tumors exhibit more aggressiveness and worse outcome if initially diagnosed at an advanced stage. The juvenile form of GCT is also typically diagnosed early, with over 90 % of cases being unilateral and stage I disease at diagnosis (Young et al. 1984). Survival has been noted to be approximately 25 % for patients diagnosed with stage II–IV disease, and recurrences of juvenile type disease typically occur early, within 3 years or less from treatment (Young et al. 1984).

2.5 Diagnosis of GCT

Diagnosis of both types of GCT is similar. Clinical suspicion might be aroused by presentations as described above, specifically evidence of hyperestrogenization, mass effects, torsion, or more acute presentation of hemoperitoneum and hypotension indicating a surgical emergency. On physical exam, these clinicians will often encounter a palpable mass on bimanual pelvic exam. Other physical exam findings would be contingent on the patient's age at diagnosis, such as breast and pubic hair development in young girls or postmenopausal vaginal bleeding in older women.

Ultrasonography often demonstrates a large adnexal mass with semisolid or echogenic features, sometimes with septations. Additionally, thickened endometrial stripe is a concerning sign in postmenopausal women (Schumer and Cannistra 2003). Cystic adult GCT, a rare variant, can appear sonographically like a benign, simple cyst, thus causing delays in management and diagnosis. Cystic adult GCT are typically thin walled and can be loculated. There is no definitive diagnostic imaging modality for these or any other type of ovarian tumor.

Tumor markers are also not diagnostic but can contribute to clinical suspicion for and subsequent surveillance of GCT. Estradiol has not been found to be a reliable marker of disease progression. Inhibin A and B have been found to be useful markers for both adult and juvenile type disease; however, they are nonspecific and can also be elevated in epithelial ovarian cancers as well as other conditions (Colombo et al. 2007).

Other important diagnostic considerations include performing an endometrial biopsy and performing breast exam and imaging due to potential sequelae from elevated levels of serum estrogen.

Definitive diagnosis requires final pathological analysis. Gross analysis typically yields a large tumor measuring 10–15 cm with dense vascular solid components. Hemorrhage and necrosis are common macroscopic findings. The most characteristic microscopic features are the "coffee bean" nuclei within granulosa cells and the Call-Exner bodies, an eosinic cystic center surrounded by rosettes of cells. Microscopic images of granulosa cell and other ovarian sex cord-stromal tumors can be found in Fig. 1a. Microscopic nodular growth patterns can also be observed in juvenile type GCT (Fig. 1b).

2.6 Genetic Alteration of GCT

Recent advances have allowed for better elucidation of the molecular components of these rare

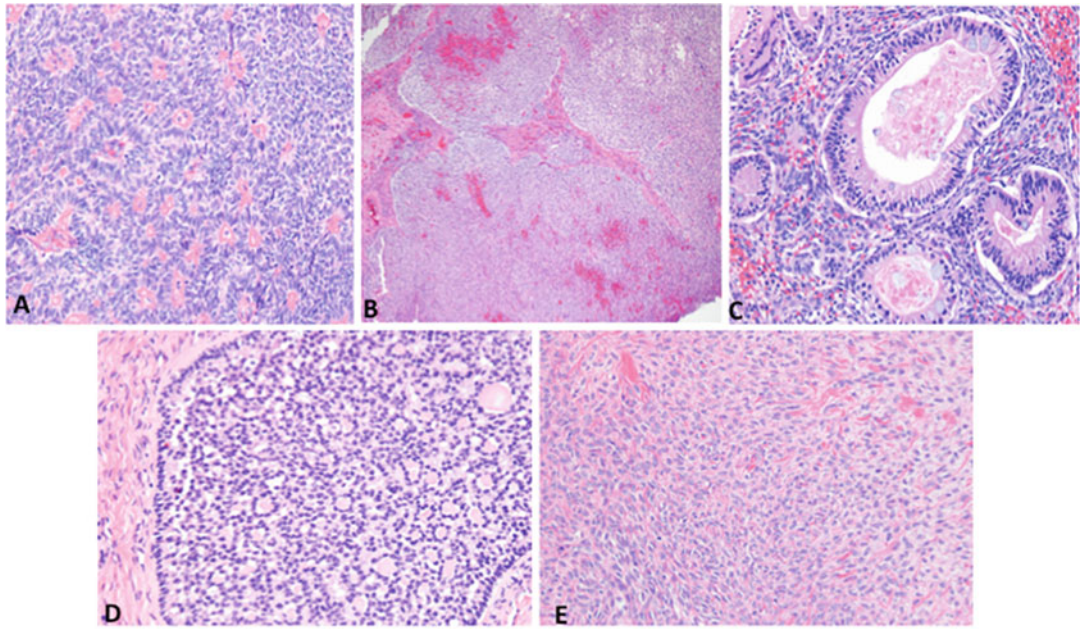

Fig. 1 Microscopic findings in sex cord-stromal tumors of the ovary ((**a**). Adult granulosa cell tumor with Call-Exner bodies (**b**). Juvenile granulose cell tumor with nodular growth (**c**). Sertoli-Leydig cell tumor with heterologous elements (**d**). Sex cord tumor with annular tubules (**e**). Fibrothecoma (Courtesy of Drs. Abby M Richmond and Miriam D Post, Department of Pathology, University of Colorado, Aurora, Colorado))

tumors. A missense point mutation in a gene encoding a transcription factor, FOXL2, has been identified in adult granulosa cell tumors, and it is thought that this mutation is likely present in all adult granulosa cell tumors (Gershenson 2012).

2.7 Sertoli-Stromal Cell Tumors

Sertoli-stromal cell tumors, or androblastomas, comprise approximately 5–10 % of all diagnosed SCSTs. There are several subtypes of tumor that fall into this category, Sertoli cell tumors and Sertoli-Leydig cell tumors, which are then characterized by the degree of tumor differentiation. These tumors typically present in reproductive age women and are almost universally unilateral. Over 90 % of Sertoli-stromal cell tumors are stage I at diagnosis (Colombo et al. 2007).

2.8 Sertoli-Leydig Cell Tumors

Sertoli-Leydig cell tumors are typically found in premenopausal women with an average age of presentation of 25. Histologically, they are formed of cells resembling stromal and epithelial testicular cells. They are frequently hormonally active, most commonly producing androgenic sex steroid hormones. Due to this, approximately 75 % of patients present with clinical evidence of virilization including temporal balding, hirsuitism, voice changes, and even clitoromegaly in rare cases (Colombo et al. 2007).

There are five histological subtypes of Sertoli-Leydig tumor based on degree of differentiation: well, intermediate, poor, retiform, and heterologous. Sertoli-Leydig cell tumors are most likely to fall into the pathological category of low malignant potential; however, those that are poorly differentiated can demonstrate aggressive behavior. Multiple review articles have examined outcome based on histological subtype. Well-differentiated tumors have uniformly benign

behavior, but poorly differentiated tumors have been shown to have malignant characteristics such as metastasis or invasion in up to 60 % of the time (Young 2005; Zaloudek and Norris 1984). Grading is based on cellular differentiation; cytologic atypia, mitotic activity, and necrosis are markers of increased risk. Survival of patients with stage I disease is greater than 90 % (Colombo et al. 2007). However, outcome is extremely poor for patients that present with disease beyond stage I with mortality being more than 90 % (Chen et al. 2003).

2.9 Genetic Alteration of Sertoli-Leydig Cell Tumors

The recent identification of an important genetic alteration called the DICER1 somatic missense mutation will allow for future research on the molecular biology of these tumors. The DICER1 codes for a domain on a component of the RNase III family, and this mutation was identified on 60 % of patients with Sertoli-Leydig cell tumors in one recent study (Gershenson 2012). The DICER1 mutation has also been identified in familial nontoxic multinodular goiter and pleuropulmonary blastoma, and both of these pathologies have been associated with increased frequency of Sertoli-Leydig cell tumors (Rio Frio et al. 2011).

2.10 Sertoli Cell Tumors

Sertoli cell tumors are formed from cellular proliferations that resemble the rete ovarii and rete testis and lack the Leydig component. The average age of presentation is 30 years. Only a quarter of these tumors demonstrate hormonal activity, which, if present, can be either estrogenic or androgenic. Sertoli cell tumors have been associated with Peutz-Jaghers syndrome (PJS) (Oliva et al. 2005). They are usually unilateral and stage I at presentation (Chen et al. 2003). Most of these tumors are well differentiated and clinically benign; however, those with atypical cytologic features are more likely to be clinically malignant (Young 2005). Pure Sertoli cell tumors are rare and there is little data on survival in patients with more advanced disease; however, there is much higher risk for distant metastasis in tumors exhibiting cytologic atypia (Oliva et al. 2005).

2.11 Diagnosis of Sertoli-Stromal Cell Tumors

Clinical suspicion for Sertoli cell tumors should be aroused if an adnexal mass is detected in a young reproductive age woman with evidence of virilization. If evidence of masculinization is present, elevated serum testosterone-to-androstenedione ratio is concerning for Sertoli-Leydig tumor. Other serum markers for an androgenically active tumor includes serum testosterone levels >150 ng/dL or dehydroepiandrosterone sulfate (DHEAS) levels >8000 μg/L (Carmina et al. 2006). However, only one half of patients will present with evidence of androgenic change; presenting symptomatic complaints in most patients will be related to mass effects of a tumor. Inhibin A and B can be useful clinical markers to follow for Sertoli-stromal cell tumors if elevated prior to surgical management.

Pathological analysis of the excised tumor is the only way to definitively diagnose these tumors. Many of these tumors have notable eosinophilic cytoplasm that is sometimes strikingly vacuolated, similar to a seminoma (Young 2005). The predominant microscopic pattern noted is tubular cells. Immunohistochemical staining is important for correctly identifying different histologic subtypes of Sertoli cell tumors as they can appear visually similar (Young 2005). Sertoli-Leydig cell tumors, which are subclassified into five levels of differentiation, have significant overlap amongst these levels of differentiation (Fig. 1c). Sertoli-Leydig tumors are sometimes described as having a distinct retiform pattern (Young 2005).

2.12 Sex Cord Tumor with Annular Tubules

Sex cord tumors with annular tubules (SCTAT) are rare, encompassing only 5 % of SCST. SCTAT are morphologically described as having components of both granulosa and Sertoli cell tumors (Fig. 1d). There are two distinct subtypes of SCTAT. Approximately one-third of SCTAT are associated with Peutz-Jaghers syndrome (PJS); these masses are typically small, bilateral, multifocal, and clinically benign.

SCTAT not associated with PJS tend to be larger and unilateral; approximately half of these tumors present with evidence of hyperestrogenization including postmenopausal vaginal bleeding, menstrual irregularities, or isosexual precocious puberty. Another distinctive characteristic is an association of SCTAT with adenoma malignum of the cervix. Adenoma malignum of the cervix, or minimal deviation adenocarcinoma, is an extremely rare well-differentiated adenocarcinoma of the cervix; this finding is only associated with SCTAT not found in conjunction with PJS. Although adenoma malignum of the cervix is a very rare finding, a review article of SCTAT found that of the four patients with this condition two of them died from it (Young et al. 1982). Approximately 20 % of these tumors are malignant.

Diagnosis of SCTAT associated with PJS is typically incidental as they are not hormonally active nor large enough to cause mass effects. Diagnosis of SCTAT not associated with PJS is similar to that of other SCST. If there are signs of hyperestrogenism, endometrial sampling is recommended to evaluate for a coincident malignant process. Also, carefully evaluate the cervix prior to surgery due to the associated with adenoma malignum.

2.13 Fibroma-Thecomas

Fibromas are typically benign masses found incidentally as they are rarely hormonally active. They originate from collagen producing cells in the ovarian stroma. They typically present in women around the age of perimenopause. They are sometimes associated with ascites. Even more rarely, they present with a clinical triad including pleural effusion, typically right sided, ascites, and a solid ovarian mass. This triad is called Meigs syndrome and is present on only 1 % of fibromas (Riker and Goba 2013). The mechanism surrounding Meigs syndrome is unclear; however, it is likely due to a large volume transudative process involving the tumor which exceeds the pertinoeum's ability to resorb the fluid (Carson and Mazur 1982). While the vast majority of these tumors are benign, approximately 10 % have nuclear characteristics, such as cytologic atypia or increased mitotic patterns, that characterize them as tumors of low malignant potential, and 1 % show evidence of transformation into fibrosarcoma and therefore warrants further treatment.

Thecomas are called such due to their characteristic appearance which resembles the theca lutein cells surrounding ovarian follicles (Chen et al. 2003). They can present at any age but present most often in postmenopausal women. These tumors are often hormonally active and present with signs of hyperestrogenization. Much like granulosa cell tumors, patients presenting with signs of excess estrogen exposure are also at risk for endometrial hyperplasia or adenocarcinoma (Aboud 1997). Less commonly these tumors are either not hormonally active or androgenic luteinizing elements are present with resulting signs of masculinization. Notably, these are benign masses and are typically unilateral.

Sclerosing stromal tumors are rare masses that also fall under the classification of fibroma-thecomas. Their characteristic presentation is that of a unilateral mass in a woman under the age of 30. They are clinically benign. Sclerosing stromal tumors are typically hormonally inactive but can present with menstrual irregularities and pelvic pain (Marelli et al. 1998).

2.14 Diagnosis of Fibroma-Thecoma

Like other ovarian masses, fibromas and thecomas are definitely diagnosed histologically after

surgical management (Fig. 1e). After initial clinical evaluation with a thorough history and physical, at which time an adnexal mass might be palpated, ultrasonography can be performed. Thecomas are uniformly solid appearing masses on ultrasound and can be mistaken as an extrauterine leiomyoma (Burandt and Young 2014). For fibromas, if the Meigs triad is present, a thoracentesis can help to evaluate for malignant pleural effusion prior to operative management. There are no specific serum markers that are relevant for fibroma-thecomas. However, cancer antigen 125 (CA125) is sometimes elevated, which can initially raise suspicion for epithelial ovarian carcinoma in the context of an adnexal mass. As with any patient presenting with postmenopausal vaginal bleeding, it is recommended that the endometrium be sampled prior to surgery if there is any concern for endometrial pathology.

2.15 Steroid Cell Tumor

Steroid cell tumors are rare, representing less than 5 % of SCST. Histologically, they resemble either testicular Leydig cells (Leydig cell tumors), adrenal cells (stromal luteomas), or steroid cell tumors not otherwise specified (NOS). Both Leydig cell tumors and stromal luteomas typically present in older, postmenopausal women. Leydig cell tumors often present with evidence of virilization, while stromal luteomas are more likely to present with postmenopausal vaginal bleeding or other evidence of hyperestrogenization. These tumors are almost universally benign; however, as with other SCSTs that are hormonally active, evaluation of the endometrium is recommended if there is concern for excess estrogen exposure.

Steroid cell tumors NOS typically present in a younger demographic and are more likely to secrete adrenal hormones such as cortisol. Women with steroid cell tumors NOS might present with a clinical characteristics mimics to Cushing syndrome, signs of which include increased abdominal adiposity, violaceous striae, moon facies, and labile mood. Approximately one-fifth of these tumors behave in a malignant fashion (Chen et al. 2003).

2.16 Gynandroblastoma

Gynandroblastomas are extremely rare. Like many SCSTs they do not demonstrate uniform cellular patterns; they typically are composed of granulosa and Sertoli components. These tumors can also present with signs of hormonal excess, and either evidence of hyperandrogenism or hyperestrogenism are possible depending on the histologic components of the tumor. The prognosis for gynandroblastoma is very good, although evidence regarding outcome is limited due to the extremely rare nature of this tumor.

2.17 Unclassified Sex Cord-Stromal Tumors

An additional category of SCST is otherwise unclassified. These are composed of an indistinct mixture of granulosa and Sertoli cells. Because they can have either ovarian or testicular cell predominance, their presentation is varied. Much like pure granulosa or Sertoli cell tumors, unclassified SCST can present with signs of virilization or hyperestrogenism. However, many of these tumors do not demonstrate hormonal activity. They behave clinically like their primary components, and outcome is typically based on the degree of morphological differentiation.

2.18 Management of Sex Cord-Stromal Tumor

Surgical resection is the foundation of treatment for SCST. However, while surgical management is the best method treatment and is often curative, it is important to tailor the treatment plan based on the patient and the specific tumor cell type. Typically, neoadjuvant chemotherapy does not have a role in treatment of SCST as these tumors are typically identified at an early stage and often aren't recognized as malignancies until intraoperative frozen section identifies them as such, especially in those tumors that are hormonally inactive.

Table 2 Tumor markers for sex cord-stromal tumor and malignant germ cell tumor of the ovary[a]

Serum marker	Associated nonepithelial ovarian tumor
Inhibin A and B	Granulosa cell tumor, Sertoli-Leydig cell tumor
Serum testosterone	Sertoli-Leydig cell tumor
Lactate dehydrogenase (LDH)	Dysgerminoma
Beta human chorionic gonadotropin (beta-hCG)	Choriocarcinoma, embryonal carcinoma
Alpha-fetoprotein (AFP)	Yolk sac tumor, embryonal carcinoma, immature teratoma
Serum squamous cell cancer antigen (SSCA)	Mature teratoma with malignant squamous transformation
Cancer antigen 25 (CA125)	Fibroma, struma ovarii, teratoma

[a]Markers will not be elevated in all cases of the associated malignancy

2.19 Preoperative Management

Considerations prior to surgery include standard preoperative work-up. Serum labs, such as complete blood count, complete metabolic panel, and type and screen, are recommended. While the blood loss is typically minimal, a type and cross ought to be considered if granulosa cell tumor is suspected due to the possibility of highly vascular nature of these tumors and associated risk for rupture and hemoperitoneum. Other preoperative considerations include systemic imaging. If there is concern for metastasis beyond the ovary alone, chest radiography or computed tomography of the chest, abdomen, and pelvis can provide more insight regarding the presence of metastatic disease. Tumor markers can be drawn prior to resection, as these can be used in surveillance and can be predictive of increased risk for recurrent disease. See Table 2 for suggested tumor markers. CA125, which is a useful marker for many epithelial ovarian cancers, has no clinical utility for SCST (Stine et al. 2013). If the patient has multiple medical comorbidities, consider referral to a primary care physician and preanesthesia services to achieve the best medical optimization possible prior to surgery.

Another integral aspect of treatment planning that can be discussed with the patient and family preoperatively is desire for future fertility. Approximately, 15 % of all ovarian cancers present in women of reproductive age, and, while the majority of SCST are diagnosed in postmenopausal women, these tumors do present frequently in young women (Gershenson 2005). As detailed above, the vast majority of SCST present unilaterally at an early stage. In this context, it is possible to consider conservative surgery in those that desire future parity. While some fertility sparing options would require assisted reproductive technology, they would allow for the potential of future biological children. Oocyte cryopreservation can also be considered since recurrence in the contralateral ovary or premature ovarian failure following adjuvant chemotherapy can occur. A consultation with a specialist in oncofertility can be offered to young women wishing to discuss options for future fertility. While management of the malignancy must supersede considerations of future fertility, it is integral to discuss the subject of future fertility with younger women prior to proceeding with surgery. In addition, benefits of ovarian sex hormone for cardiovascular, bone, and cognitive health aspects in young premenopausal women need to be considered.

If a malignancy is suspected, a consultation with a gynecologic oncologist prior to operative management is suggested. Due to the rare nature of SCST and the fact that they are often not hormonally active, there are a significant number of these tumors that are identified intraoperatively or on pathology postoperatively. It is beneficial to have the potential for frozen pathology analysis if concerning tumor characteristics are encountered intraoperatively.

2.20 Surgical Management

Surgical management with complete cytoreduction if metastases are present will provide the patient with the best outcome

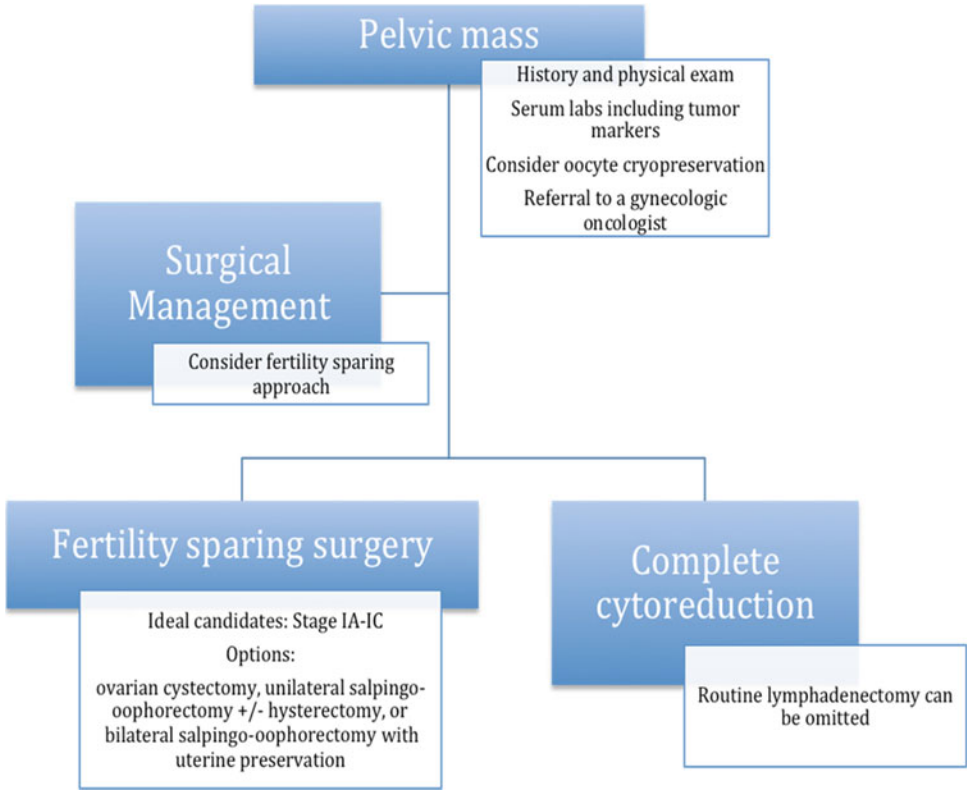

Fig. 2 Principles of surgical management for sex cord-stromal tumors of the ovary

(Gershenson 2012). Surgical approach will vary based on patient and disease characteristics. Minimally invasive approaches are often appropriate for presumed stage I disease; however, if there is tumor rupture this will result in upstaging and potentially necessitate further treatment. Open approaches allow more access for complete cytoreduction in more advanced stage disease, which can be anticipated based on clinical exam and imaging findings.

The decision to proceed with surgical staging will be based on frozen section results and intraoperative findings. If the tumor is not a malignant SCST, comprehensive staging can be omitted. Thus, if the pathology is positive for a benign lesion, then the surgery can be completed without further staging. However, it must be remembered that frozen pathology is not infallible, and accuracy may be decreased in the setting of rare tumors such as SCST (Covens et al. 2012). If staging was not performed at the time of an initial surgery, an additional staging procedure may be completed if indicated by malignancy results on permanent pathology and systemic imaging suggests suspicion for metastasis. Figure 2 provides recommendations for the initial surgical management of SCST.

Surgical staging can be completed via minimally invasive approach or open laparotomy. Staging consists of a thorough exploration of the abdomen and pelvis, collection of pelvic washings, peritoneal biopsies and partial omentectomy as well as cytoreduction any visible tumor including hysterectomy and bilateral salpingo-oopherectomy in women not wishing to maintain reproductive potential. The role of routine lymphadenectomy in staging SCST has been debated. Lymphadenectomy has not been shown to improve survival in SCST, and the procedure can be associated with increased postoperative complications including lymphocele or lymphedema (Gershenson 2012). The National

Comprehensive Cancer Network (NCCN), which articulates treatment guidelines for malignancies in the United States, specifies that routine lymphadenectomy can be omitted during the staging of SCST (Morgan 2015).

As above, the desire for future fertility can be discussed prior to proceeding with operative management. In the absence of advanced disease, fertility sparing surgery is an acceptable management option for women with stage IA to IC disease (Morgan 2015). Procedures considered fertility sparing include ovarian cystectomy, unilateral salpingo-oopherectomy with or without coincident hysterectomy, or bilateral salpingo-oopherectomy with uterine preservation (Gershenson 2005).

2.21 Postoperative Management

The decision to proceed with additional treatment versus expectant management is dependent on stage and, sometimes, tumor characteristics. Guidance on postoperative treatment is shown in Fig. 3. The most common postoperative treatment options utilized are either observation or platinum-based chemotherapy. Tumor markers, if elevated at the time of presentation, are a relatively noninvasive way to monitor for recurrence. Radiotherapy is of limited use for SCST but can be used for palliative purposes.

As with surgical management, fertility desires can be discussed prior to initiation of chemotherapy. Cryopreservation can be considered before starting chemotherapy, especially since platinum-based modalities are known to be especially toxic to oocytes. Cryopreservation also allows for fertility in the context of recurrent disease on the contralateral ovary if fertility sparing surgery has been performed.

2.22 Low-Risk Disease

For stage IA disease, the prognosis is excellent; so, no further treatment is recommended (Morgan 2015). Surveillance, consisting of pelvic exams and serum tumor marking testing if initially elevated, should occur every 2–4 months for the first 2 years following surgery, then every 6 months

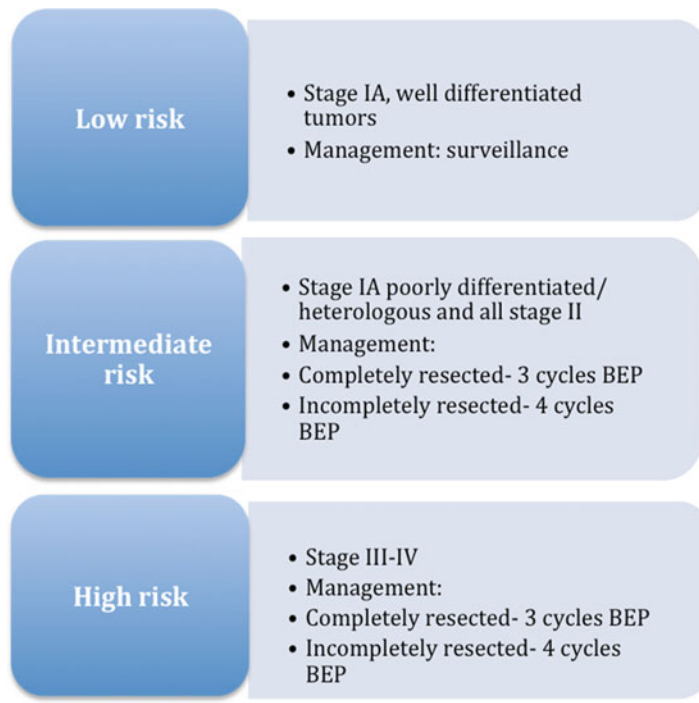

Fig. 3 Adjuvant therapy for sex cord-stromal tumors

thereafter (Salani et al. 2011). Systemic imaging is indicated if recurrence is suspected.

2.23 Intermediate-Risk Disease

For disease diagnosed at a higher stage, there is still debate over optimal management. Intermediate-risk stage I disease is classified based on characteristics such as tumor rupture, large tumor size, high mitotic rate, positive cytology, heterologous elements, poorly differentiated tumor, or incompletely staged disease (Morgan 2015). Any stage II disease also falls into the category of intermediate risk. The current consensus recommends either observation, with surveillance as detailed above, or platinum-based chemotherapy (Morgan 2015). The preferred adjuvant regimen is either platinum plus taxane or bleomycin, etoposide, and cisplatin (BEP). The most commonly used first line regimen is the 5-day BEP course because it has the highest known response rate (Homesley et al. 1999). Three cycles administered every 3 weeks is recommended for completely resected disease, but one additional cycle is recommended for patients with incompletely resected disease (Homesley et al. 1999).

2.24 High-Risk Disease

Adjuvant chemotherapy is definitely recommended for higher risk patients including stage III to IV disease. The same regimen of BEP as that detailed for intermediate-risk disease is recommended. Thus, for completely resected disease, three cycles is adequate treatment, while administering four cycles is recommended for incompletely resected disease.

2.25 Surveillance

Risk of recurrence remains high even years after surgical resection and adjuvant treatment. According to the NCCN guidelines, surveillance consists of office visits every 2–4 months for 2 years following completion of treatment. These visits will include a pelvic exam and serum tumor markers if initially elevated. Imaging can be performed in the context of a suspected recurrence. There is no role for routine serum tumor markers or imaging without suspicion for recurrence. After 2 years, surveillance visits should occur every 6 months (Morgan 2015).

2.26 Recurrent Disease

Disease can recur after long periods of remission, which is why continued surveillance at 6-month intervals is recommended after the initial 2-year period. Currently, there are no definitive guidelines for recurrent disease. Secondary cytoreduction is considered in cases with limited disease volume. Combination platinum-based chemotherapeutic regimens are typically considered first-line therapy whether or not secondary debulking is performed; BEP is administered most frequently due to its high response rate (Homesley et al. 1999). Other acceptable recurrence therapy options as designated by the NCCN include aromatase inhibitors, bevacizumab (for GCT), taxane, taxane plus ifosfamide, taxane plus carboplatin, tamoxifen, vincristine plus dactinomycin plus cyclophosphamide, radiation, or supportive care only (Morgan 2015). Possible novel strategies include hormonal therapy, such as aromatase inhibitors or the gonadotropin-releasing hormone agonist, leuprolide, for granulosa cell tumors (Morgan 2015). While promising, these treatment methodologies are still under investigation. The identification of germline mutations, such as FOXL2 mutations, may allow for exploration of targeted therapeutics. Thus far, there has been investigation of ketoconazole, the cytochrome P17 (CYP17) inhibitor, as a treatment modality for recurrent granulosa cell tumors due to the recognition that FOXL2 downregulates CYP17 (Garcia-Donas et al. 2013). Because this is based on case report, further studies are warranted. The antiangiogenic bevacizumab has been shown to have moderate activity against recurrent OSCST; more studies involving vascular endothelial growth factor

inhibitors are currently underway (Gershenson 2012).

2.27 SCST in Pregnancy

Although a rare phenomenon, SCST does occur coincident with pregnancy. Mirroring the incidence of SCST outside of pregnancy, the most commonly encountered histological subtype is granulosa cell. Notably, a rate of serious adverse events including hemoperitoneum and maternal shock was observed to be greater than 40 % in a recent review of pregnancies complicated by SCST (Blake et al. 2014). Therefore, pregnancy complicated by suspected SCST is characterized as a high-risk pregnancy and managed in conjunction with gynecologic oncology and maternal-fetal medicine specialists. Survival of patients with SCST diagnosed within the context of a pregnancy seems comparable to those diagnosed not related to pregnancy, even when managed conservatively (Blake et al. 2014). Management of pregnancy complicated by SCST is not standardized; however, fetal preservation surgery, especially if undertaken in the second trimester, is a reasonable option associated with good maternal and fetal outcomes.

3 Ovarian Malignant Germ Cell Tumors

3.1 Pathogenesis

Germ cell tumors are cancers that originate from primordial germinal cells. Germ cell tumors of the ovary are most often benign, with malignant tumors representing only 5 % of germ cell diagnoses. Malignant germ cell tumors comprise only about 2–3 % of all ovarian malignancies (Quirk and Natarajan 2005). Ovarian germ cell tumors can be further classified into primitive germ cell tumors, differentiated germ cell tumors, and mixed tumor types as described in Table 3. This chapter will address malignant variations of germ cell tumors including dysgerminoma, immature teratoma, yolk sac tumor, polyembryoma, choriocarcinoma, embryonal carcinoma, and mixed germ cell tumor. The most common germ cell tumor is the mature cystic teratoma, or dermoid cyst, and, while typically benign, cellular components of the dermoid can undergo malignant transformation. In general, ovarian malignant germ cell tumors (OMGCT) present in women under age 30. Depending on the subtype, malignant germ cell tumors can demonstrate hormonal activity.

Table 3 World Health Organization histologic classification for germ cell tumors of the ovary

Primitive germ cell tumors
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma
Polyembryoma
Nongestational choriocarcinoma
Teratomas
Immature
Mature solid
Mature cystic (dermoid)
Monodermal
Mixed forms

The molecular pathogenesis of OMGCT is currently under investigation. Specific microRNA clusters were noted to be overexpressed in all OMGCT. Notably, after a patient with yolk sac tumor was successfully treated, these clusters returned to a normal level (Gershenson 2012). Additionally, the KIT oncogene, a tyrosine kinase receptor recognized as a proto-oncogene in multiple malignancies, has been identified in dysgerminomas, especially those at advanced stage (Gershenson 2012).

3.2 Dysgerminoma

Dysgerminomas are traditionally the most common malignant germ cell neoplasm, but incidence is reported to be decreasing proportionally to other germ cell malignancies in recent years (Smith et al. 2006). These tumors are the "prototypical" germ cell tumors, meaning they are composed of cells that resemble primordial germ cells

and appear histologically very similar to seminomas originated from testicular cells. Unlike other types of germ cell tumors, dysgerminomas cannot further differentiate (Chen et al. 2003). These tumors present bilaterally in approximately 15 % of cases.

Historically, the prognosis for dysgerminoma was dismal; however, due to their chemosensitivity, overall survival is now greater than 99 % (Chan et al. 2008). Over two-thirds of patients present at stage I; however, even later stage disease has an excellent prognosis. Notably, dysgerminomas often spread lymphatically, and approximately one quarter of dysgerminomas are found to have metastasized to regional lymph nodes at the time of diagnosis (Kumar et al. 2008).

3.3 Diagnosis of Dysgerminoma

If an adnexal mass is identified in a young woman, malignant germ cell tumors can be considered in the differential diagnosis. Since these tumors occur bilaterally in approximately 15 % of cases, careful attention during the exam of the contralateral ovary after a mass is appreciated. The most common presenting symptom is vague abdominal or pelvic pain due to mass effect. However, acute presentations can occur if the mass torses or ruptures causing hemoperitoneum.

Notably, dysgerminomas are found disproportionately in the context of gonadal dysgenesis. Females with karyotypically abnormal gonads, such as those with Turner syndrome (45X/46XY) or Swyer syndrome (46XY), are at risk for developing a gonadoblastoma. While gonadoblastomas are benign lesions, approximately 40 % of these masses undergo malignant transformation, often into dysgerminomas (Pena-Alonso et al. 2005). Young women presenting with abnormal bleeding patterns and pelvic masses should be carefully evaluated for the presence of gonadal dysgenesis. If there is concern for gonadal dysgenesis, a karyotype can be performed.

Imaging via ultrasonography is another important component of the evaluation of a patient with an adnexal mass. Typically these present as solid masses on imaging. Ultrasound characteristics include a well-defined mass divided into component lobules with color Doppler demonstrating rich vascularization (Shaaban et al. 2014). Computed tomography (CT) also demonstrates a mass that is solid and potentially septated with scattered calcifications (Shaaban et al. 2014). CT can also demonstrate sequelae of advanced disease including ascites or evidence of distant metastases or lymphadenopathy.

Tumor markers can also be elevated in the presence of dysgerminoma. Typically these tumors are not hormonally active; they can contain syncytiotrophoblasts which cause serum beta-human chorionic gonadotropin (beta-hCG) elevations. Additionally, serum levels of lactate dehydrogenase (LDH) can also be elevated in the presence of dysgerminoma. While LDH is not specific, it can be a useful serum marker for recurrence if elevated initially.

As with any malignancy, definitive diagnosis cannot be made until final pathology is reviewed. These tumors are typically solid and white or gray in macroscopic appearance. Microscopically, these tumors resemble testicular cancers. Cells are round and uniform, usually surrounded by fibrous stranding or T lymphocyte infiltration (Fig. 4a).

3.4 Yolk Sac Tumors

Yolk sac tumors, previously called endodermal sinus tumors, are composed of remnants of the primitive yolk sac or vitelline elements. These tumors characteristically grow rapidly, and they typically present at a young age, rarely occurring in women over the age of 40. While yolk sac tumors are generally unilateral, they are more aggressive than most other germ cell tumors. Not only do yolk sac tumors demonstrate rapid growth, distant disease is often noted at presentation. The most common sites of metastasis include the lungs and local peritoneal spread (Chen et al. 2003).

Due to their aggressive characteristics, yolk sac tumors have the worst prognosis of all germ cell malignancies. Almost half of the cases of yolk sac

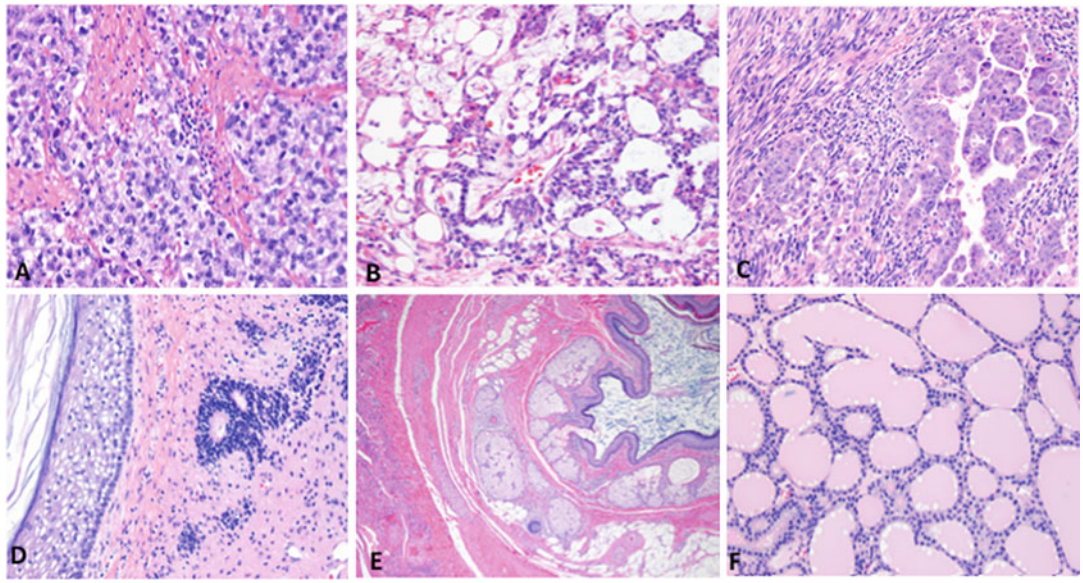

Fig. 4 Microscopic findings of malignant germ cell tumors of the ovary ((**a**). Dysgerminoma (**b**). Yolk sac tumor with Schiller-Duval bodies (**c**) Embryonal carcinoma (**d**). Immature teratoma with rosette (**e**). Mature cystic teratoma (**f**). struma ovarii (Courtesy of Drs. Abby M Richmond and Miriam D Post, Department of Pathology, University of Colorado, Aurora, Colorado))

tumor present after advancing beyond stage I disease. Even with appropriate treatment, survival rate for patients with stage III-IV disease is 50–75 %. However, 5-year survival rate for patients with only stage I disease is greater than 90 % (Chan et al. 2008). According to recent data, recurrences usually present within a year following treatment and are typically not responsive to further therapy (Cicin et al. 2009).

3.5 Diagnosis of Yolk Sac Tumor

Since yolk sac tumors typically grow rapidly, women with these tumors often complain of relatively acute onset abdominal or pelvic pain. Review articles have noted several cases with growth of masses measuring greater than 20 cm over the course of weeks to months (Kurman and Norris 1976). Capsular rupture is fairly common, likely because of the rapid expansion of these tumors. These patients can also present with hemoperitoneum as these rapidly growing lesions are highly vascularized. If a large mass is palpable on pelvic exam, especially in a young premenopausal woman, suspicion for a yolk sac tumor is increased.

Imaging can be obtained after appreciation of a mass on exam. Ultrasound findings can include a unilateral mass with heterogenous echogenicity and septations. Computed tomographic images are often significant for enhancing foci in the tumor wall attributable to dilated blood vessels. Capsular tears can also sometimes be appreciated on imaging. None of these findings is pathognomonic for yolk sac tumors; however, they can help contribute to heightened preoperative suspicion for this entity (Shaaban et al. 2014).

Serum tumor markers can also be helpful in both preoperative evaluation for yolk sac tumors and for postoperative surveillance. These tumors produce alpha-fetoprotein (AFP). AFP is not specific for yolk sac tumors as other germ cell malignancies can produce this protein that is typically found in fetal circulation; however, yolk sac tumors will almost universally have elevated AFP level.

Pathological analysis is required for definitive diagnosis. Gross pathology will be significant for a large mass, on average measuring 15 cm, with

mixed solid and cystic components. There are often focal areas of hemorrhage and necrosis in macroscopic appearance. Microscopically, these tumors can vary significantly in appearance; however, by definition they resemble the cellular structure of the primitive yolk sac. The appearance of an isolated papillary body containing a centralized vessel and surrounded by embryonic epithelial cells, called a Schiller-Duval body, is pathognomonic for yolk sac tumor but is not required for diagnosis (Fig. 4b).

3.6 Embryonal Carcinoma, Polyembryona, and Mixed Germ Cell Tumor

Other rare subtypes of primitive germ cell tumors include embryonal carcinoma, polyembryona, and mixed germ cell tumor. While all of these variants are likely to present in somewhat mixed form, they each have specific characteristics that allow them to be classified as individual entities.

Embryonal carcinoma is another malignant variant that can evolve from dysgenetic gonads. These tumors typically present in girls in their teenage years. Embryonal carcinoma typically produces beta-hCG and often produces AFP. On pathology, these tumors are noted to have solid sheets of anaplastic cells and distinctive papillary projections (Ulbright 2005; Fig. 4c).

Polyembryonas are extremely rare. These tumors have features of both primitive and differentiated germ cell tumor types, so are sometimes considered to be extremely immature teratomas (Ulbright 2005). Serum AFP and beta-hCG are often elevated in the presence of these tumors. Polyembryonas almost exclusively present as components of mixed germ cell tumor. Microscopically, these tumors have central "germ discs" surrounded by two cavities, one resembling the amniotic cavity and the other resembling the yolk sac cavity (Ulbright 2005).

Ovarian mixed germ cell tumors contain aspects of multiple types of germ cell tumors without one predominant component. Dysgerminoma is the most common component of mixed germ cell tumors, but they can contain elements of any histological subtype. The presence of higher risk malignant elements, such as high-grade immature teratoma, increases the likelihood of aggressive behavior.

3.7 Nongestational Choriocarcinoma

Nongestational choriocarcinoma in pure form is very rare, accounting for less than 5 % of malignant germ cell tumors (Smith et al. 2006). These are aggressive tumors which can be confused with metastatic gestational choriocarcinoma. Gestational choriocarcinoma is associated with a proximate pregnancy and can metastasize to the ovaries. This distinction is important due to the poorer prognosis of nongestational choriocarcinoma (Corakci et al. 2005). The distinction between these two entities is made based on pathology findings; nongestational choriocarcinoma will be found in the presence of other germ cell components (Ulbright 2005).

These tumors are typically found in patients less than 20 years. Information on prognosis is limited due to the extremely rare nature of this tumor; however, prognosis is typically poor due to the frequency of distant metastasis at presentation (Corakci et al. 2005). Beta-hCG is often markedly elevated in these patients. The elevated beta-hCG can result in prominent symptoms such as isosexual precocious puberty or menstrual abnormalities in women who have undergone menarche.

3.8 Teratoma

All teratomas consist of components from all three germ cell layers: endoderm, mesoderm, and ectoderm. The malignant variation of teratoma is termed immature, but the majority of these tumors are classified as mature. Although rare, malignancy can develop within a mature cystic teratoma. The term dermoid is often used interchangeably with teratoma; however, there is a histological distinction between the two entities. Dermoids are composed of epidermal and dermal

elements, while teratomas contain mesodermal and endodermal components. Teratomas can also be classified as monodermal or specialized when they consist predominantly of endodermal or ectodermal elements.

3.9 Immature Teratoma

Immature teratomas account for 30 % of deaths from ovarian malignancy in women under age 20. They are now the most commonly detected malignant germ cell tumor (Smith et al. 2006). In addition to endodermal, mesodermal, and ectodermal components, they also contain embryonic tissue, thus qualifying them as immature. These tumors typically present in women in their teenage years and rarely occur in postmenopausal women. Immature teratomas are typically unilateral but often have spread via local peritoneal seeding or via lymphatics at the time of diagnosis. If bilateral, which occurs in about 10 % of cases, the contralateral tumor is generally a mature teratoma. The typical size at presentation is 14–25 cm (Wisniewski and Deppisch 1973).

Despite immature teratomas having a propensity to disseminate early, approximately three-quarters of these tumors are detected at stage I. The 5-year overall survival for stage I disease is greater than 95 %. Survival for later stage disease is associated with poorer prognosis, but overall survival is still relatively high, ranging from 73 % to 88 % (Chan et al. 2008). Recurrence is not uncommon, but recurrent disease typically remains chemosensitive.

A phenomenon specific to immature teratoma is that of growing teratoma syndrome, which refers to postoperative growth of mature teratoma elements implanted in the peritoneum. These implants are typically benign and chemoresistant and can continue enlarging so resection is required to exclude recurrent malignancy. The incidence is relatively low, approximately 12 % (Zagame et al. 2006). Prognosis is generally not affected by the presence of growing teratoma syndrome.

3.10 Mature Teratoma with Malignant Transformation

Mature cystic teratomas are the most common benign ovarian neoplasm and typically present in women age 20–40. These masses typically measure approximately 7 cm at presentation (Wisniewski and Deppisch 1973). Malignant transformation occurs very rarely in mature cystic teratomas, and it typically presents in postmenopausal women. The incidence of malignant transformation is approximately 1–2 % (Smith et al. 2006). The most commonly identified malignancy is squamous cell carcinoma, which accounts for about 80 % of malignant transformations. There is no clear mechanism of malignant transformation identified; however, it is notable that the average age of presentation is approximately 50 years, while most mature cystic teratomas are diagnosed in women several decades younger (Dos Santos et al. 2007). This finding has led to the hypothesis that prolonged presence of teratomas in situ increases the likelihood of malignant transformation; therefore, even though typically benign, it is important to surgically remove these masses. Unfortunately, the prognosis for squamous cell carcinoma within mature cystic teratoma is low as 48 % overall; 5-year survival for stage IV disease is reported as 0 % in one study (Chen et al. 2008). Other malignancies that have been reported within mature cystic teratomas include melanoma, basal cell carcinoma, thyroid carcinoma, carcinoid, chondrosarcoma, leiomyosarcoma, angiosarcoma, and intestinal adenocarcinoma (Chen et al. 2003).

3.11 Malignant Struma Ovarii

Struma ovarii refers to a type of monodermal teratoma that is composed of at least 50 % thyroid tissue. Struma ovarii accounts for approximately 3 % of mature teratomas (Roth and Talerman 2007). These tumors are typically benign, but a malignant component presents in less than 5 % of cases of struma ovarii. Carcinomas that can occur within malignant struma ovarii include follicular

or papillary variants. Additionally, struma ovarii can contain nonthyroid type neoplasms including carcinoid, Brenner tumor, or mucinous cystadenoma. These tumors typically present in postmenopausal women.

3.12 Paraneoplastic Encephalitis

Although not a malignancy, *N*-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an important phenomenon associated with ovarian teratomas. NMDA receptor antibody encephalitis is a paraneoplastic neurologic syndrome characterized by psychiatric symptoms, seizures, amnesia, and semirepetitive dystonic movement abnormalities. While a mass is not always present, the syndrome is most classically associated with teratomas in young women. Positive serum NMDA receptor antibody titers in the presence of this constellation of symptoms is diagnostic, and typically a higher antibody titer correlates with more severe symptoms (Irani and Vincent 2011). The pathogenesis of this condition is not fully understood; however, it is thought that impaired immunomodulation in the context of a disrupted blood–brain barrier could be responsible for the paraneoplastic syndrome (Irani and Vincent 2011). Treatment is centered on decreasing antibody levels both via surgical resection and pharmacologic agents including corticosteroids, plasma exchange, and intravenous immunoglobulins. Early resection and treatment are noted to have the best outcomes; death or permanent neurological sequelae can occur in the absence of prompt recognition and treatment (Irani and Vincent 2011).

3.13 Diagnosis of Teratoma

Most teratomas will be diagnosed either incidentally or after palpation of an adnexal mass as there are typically few systemic sequelae. Some patients will present complaining of vague abdominal or pelvic pain. Mature teratomas also commonly present with symptoms of torsion including intermittent visceral abdominal pain or pressure and nausea or vomiting. Patients with struma ovarii present with clinical hyperthyroidism in approximately 5 % of cases (Roth and Talerman 2007). Additionally, struma ovarii presents with ascites in one-third of cases and with Meigs syndrome in rare cases (Roth and Talerman 2007). Meigs syndrome is a clinical triad consisting of ascites, pleural effusion, and pelvic mass.

On imaging, teratomas appear as heterogenous solid adnexal masses, often described as a cystic mass with intratumoral fat. Classically, mature teratomas are described as having a "dot-dash" pattern on ultrasound. Small areas of cystic calcifications or fatty elements can be appreciated on ultrasound. In immature teratomas, these calcified areas appear small, irregular, and scattered, while calcifications appear more well-defined or even tooth-like in mature teratomas (Shaaban et al. 2014). Another common ultrasound finding in mature teratomas is the Rokitansky nodule or dermoid plug, which is a nodule containing hair, teeth, and fat. If present, malignant transformation can occur in the region of the Rokitansky nodule and is seen as a heterogenous irregular solid mass that might demonstrate invasion into surrounding tissue (Shaaban et al. 2014). Cystic components have attenuation and signal intensity similar to that of simple fluid in immature teratomas but will appear more as fatty sebaceous material in mature teratomas on CT imaging (Shaaban et al. 2014).

Although no tumor marker is characteristic for teratomas, there are several that can be present depending on the predominant cell types contained within the teratoma. Serum markers such as AFP, CA125, cancer antigen 19-9 (CA19-9) can be elevated in immature teratomas (Li et al. 2002). If elevated, these markers can assist in postoperative surveillance. Another useful tumor marker evaluating for the presence of malignant transformation of a mature teratoma is serum squamous cell carcinoma antigen (SSCA). SSCA has been shown to be elevated in greater than 80 % of patients that have foci of squamous cell carcinoma (Chen et al. 2008). Elevated CA125 can be found in the context of struma ovarii. While most patients with struma ovarii

are chemically and clinically euthyroid, there can be abnormalities in thyroid hormone levels.

While the above factors can help assist in diagnosis and surveillance, final pathology is required for definitive diagnosis. Microscopically, components of all three germ cell layers can be observed in both immature and mature teratomas (Fig. 4d). Immature teratomas typically appear as disordered mixed tissue (Fig. 4e). Tumor grade or aggressiveness is dependent on the amount of immature neural tissue contained within the tumor. Teratomas grossly contain hair, fatty or sebaceous material, and calcifications or teeth; immature teratomas tend to be larger in diameter than mature teratomas. Struma ovarii is formed of mature thyroid tissue and grossly appears as brown- or amber-colored colloidal material with thick septations (Fig. 4f).

3.14 Management of Ovarian Malignant Germ Cell Tumors

Historically, malignant germ cell tumors were associated with an abysmal prognosis. However, the development of modern chemotherapeutic techniques has drastically improved outcomes for these tumors. Initial surgical cytoreduction remains the cornerstone of management for malignant germ cell tumors. Surgery and resulting pathology findings are both therapeutic and diagnostic. Neoadjuvant chemotherapy has little clinical utility in OMGCT.

3.15 Preoperative Evaluation

Thorough preoperative assessment includes a consideration of preoperative imaging to evaluate for evidence of distant metastasis and thus aid in surgical planning. Preoperative labs including complete blood count, complete metabolic panel, and type and screen can be drawn prior to any potential major abdominal surgery. Tumor markers including LDH, b-HCG, AFP, CA125, CA19-9, and SSCA can be considered. Appropriate tumor markers are to be selected based on presentation and clinical suspicion for specific subtypes of OMGCT. The age of incidence for OMGCT is typically younger than that of other malignancies, so medical comorbidities necessitating preoperative anesthesia clearance are less common in this demographic; however, preanesthesia evaluation can be taken into consideration.

It is important to discuss implications of surgery and subsequent chemotherapy with patients and their families prior to undertaking the procedure. Since OMGCT often presents in women of reproductive age, a discussion of future fertility desires is recommended. Although management of the present malignancy must take precedence over future fertility desires, current literature indicates that patients and their families appreciate this discussion and may even be unaware prior to the procedure that loss of fertility or changes in future hormonal status could be a result of treatment (Loren et al. 2013). Due to excellent outcomes, fertility sparing surgery is now considered standard of care for OMGCT (Gershenson 2012). Oocyte cryopreservation is also a potential option for patients wishing to preserve future fertility. Adjuvant chemotherapy and risk of relapse in the remaining ovary are concerns to potential future fertility; as such, oocyte harvesting can help to ensure better reproductive outcomes in the future. There are multiple options available for young women wishing to preserve their future fertility in the context of malignancy, and, if available, referral to a specialist in oncofertility can be offered.

There is a high rate of relapse after inadequate staging and follow-up of OMGCT (Gershenson 2012). Therefore, for cases in which there is high suspicion for one of these malignancies, a referral to a gynecologic oncologist for staging and management is recommended.

3.16 Surgical Management

Surgical approach is dictated based on tumor and patient characteristics. Whenever possible, surgical spill should be avoided in order to prevent iatrogenic upstaging of disease. Many OMGCT are large at the time of presentation and thus

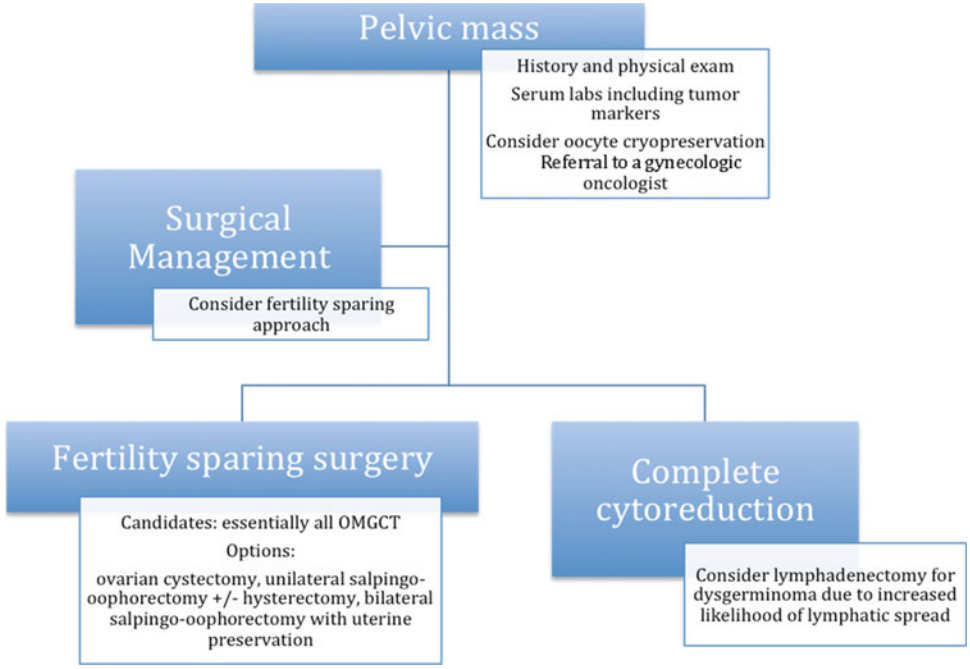

Fig. 5 Principles of surgical management for malignant germ cell tumors of the ovary

preclude minimally invasive surgical options. However, if possible, the reduced postoperative morbidity of laparoscopic surgery compared to laparotomy is favorable if adequate staging is allowed through this approach. Surgeons consider low threshold to convert from laparoscopy to laparotomy when surgical spill is concerned for the tumor grossly confined in the ovary. See Fig. 5 for recommendations regarding surgical management for OMGCT.

The exact extent of appropriate surgical staging for apparent early stage OMGCT remains somewhat contentious. Procedures considered fertility sparing include ovarian cystectomy, unilateral salpingo-oopherectomy with or without coincident hysterectomy, or bilateral salpingo-oopherectomy with uterine preservation (Gershenson 2005). Pediatric literature recommends conservative staging consisting of examination of peritoneal surfaces and collection of washings, palpation of retroperitoneal lymph nodes, and biopsy of abnormal appearing areas following resection of the affected ovary and visible mass (Billmire et al. 2004). A longitudinal review of oncologic and fertility outcomes for pediatric patients that underwent fertility sparing surgery and adjuvant chemotherapy found favorable outcomes regardless of histologic subtype and FIGO stage (Park et al. 2015). Additionally, fertility sparing surgery in the aforementioned study was conservatively defined as preservation of the unaffected ovary and uterus.

Bilateral tumors are present in less than 10 % of OMGCT; however, they present a challenge to those wishing to preserve fertility. Although literature for the rare presentation of bilateral malignancies is minimal, available studies indicate that these tumors have a good prognosis and that fertility preservation can be considered, especially in the setting of bilateral dysgerminoma (Sigismondi et al. 2015). In a small study examining outcomes of bilateral OMGCT of various subtypes, a unilateral salpingo-oophorectomy was performed along with either a biopsy or cystectomy on the contralateral ovary followed by treatment with chemotherapy. The small subset of four patients treated with ovarian preservation demonstrated resultant preservation of future fertility and similar survival outcomes to those patients that were completely staged (Sigismondi et al. 2015). This data is based

on very limited case numbers and risks and benefits ought to be considered carefully before deciding to leave an affected ovary in situ.

Traditional practice endorses that, similar to those with epithelial ovarian cancers, patients receiving complete cytoreduction improves survival outcome (Suita et al. 2002). However, as supported by the data above, accumulating evidence endorses a less aggressive staging procedure even if fertility preservation is not a priority of management. A careful inspection of all intraabdominal and pelvic surfaces is necessary. If tumor histology is identified on frozen pathology, characteristic patterns of dissemination are to be taken into consideration. Dysgerminomas demonstrate lymphatic spread more frequently than other types of OMGCT, and this can be taken into consideration when deciding whether or not to perform staging with lymphadenectomy. Yolk sac tumors and immature teratomas are more likely to spread locally and have metastases present on the peritoneum and omentum. In advanced disease, the aim of surgery is maximally cytoreducing all accessible tumors.

4 Postoperative Management

4.1 Adjuvant Chemotherapy

OMGCT are typically notably chemosensitive. The responsiveness to chemotherapy allows surgical treatment to be less aggressive and allows for fertility sparing treatment as above. OMGCT, especially dysgerminoma, are often radiosensitive, and radiation was used in the past to treat these tumors but is no longer standard of care. Combination chemotherapy regimens including vincristine, dactinomcycin, cyclophosphamide (VAC) or cisplatin, vinblastine, bleomycin (PVB) were introduced in the 1970s with marked improvement in outcomes for patients diagnosed with OMGCT. Currently, all histologic subtypes of these tumors are treated with a combination of bleomycin, etoposide, and cisplatin (BEP), as this regimen was found to be more active and had an acceptable toxicity in patients (Gershenson et al. 1990). BEP is now first line for adjuvant therapy. Figure 6 outlines basic principles of postoperative management of OMGCT.

Current standard of care includes postoperative chemotherapy for all patients except those with well staged stage IA, grade 1 pure immature

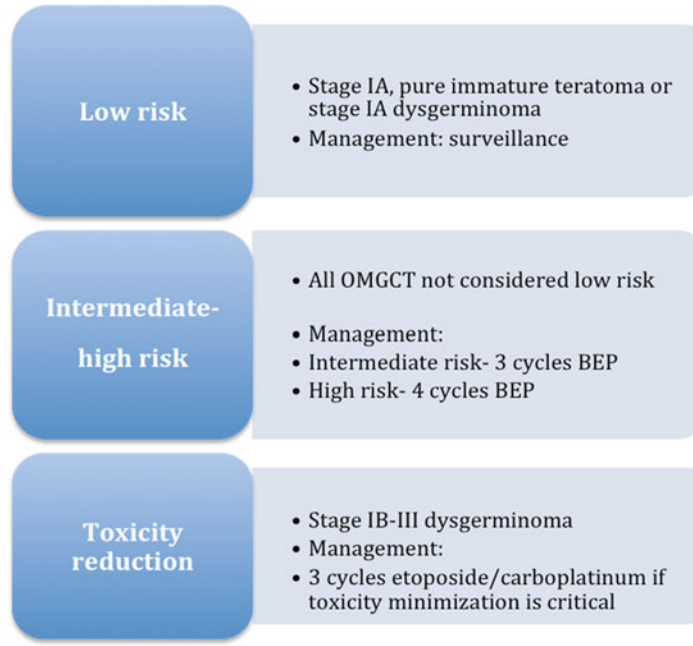

Fig. 6 Adjuvant therapy for malignant ovarian germ cell tumors

teratoma or stage I pure dysgerminoma. BEP is typically administered every 3 weeks. Randomized control trials have demonstrated that three cycles is adequate to prevent recurrence in nearly all patients who have undergone staging with complete cytoreduction (Williams et al. 1994). NCCN guidelines recommend three cycles for patients considered low risk for recurrence and four cycles for higher risk disease (Morgan 2015). Pulmonary function tests are recommended prior to starting bleomycin. Alternatively, the NCCN specifies that three courses of carboplatinum and etoposide can be used to reduce toxicity if the diagnosis is stage IB-III dysgerminoma (Morgan 2015). This regimen is administered every 4 weeks for 3 cycles.

Many patients and families will express concern about the effects of chemotherapy on future fertility. Unlike radiation treatment, the majority of patients receiving the standard BEP regimen resume normal menses and have successful future fertility outcomes (Weinberg et al. 2011). As above, oocyte cryopreservation will allow for improved fertility outcomes for the minority patients that experience premature ovarian failure following BEP.

4.2 Surveillance

Risk of recurrence is highest in the first few years following surgical resection. According to the NCCN guidelines, surveillance consists of office visits every 2–4 months for 2 years following completion of treatment (Morgan 2015). These visits include a pelvic exam and serum tumor markers if initially elevated. Imaging can be performed in the context of a suspected recurrence. There is no role for routine serum tumor markers or imaging without suspicion for recurrence. After 2 years, annual exams can be performed (Salani et al. 2011).

4.3 Recurrence

Rates of recurrence vary depending on histological subtype, disease stage, and extent of the initial cytoreduction. As above, there remains controversy about the extent of surgical staging that is recommended with the initial tumor reduction surgery. Fortunately, even in the event of recurrent disease, the overwhelming majority of patients are salvageable.

The NCCN guidelines recommend referral to a tertiary center for management of recurrent disease (Morgan 2015). There are multiple options for recurrent disease, but there are no definitive guidelines. The NCCN recommends either high-dose chemotherapy, the specifics of which can differ among institutions, or another choice of combination regimens, most of which include a platinum agent (Morgan 2015). Platinum agents are not recommended if the tumor is platinum resistant or recurrent within 6 months of completing initial treatment. There is negligible role for secondary cytoreduction if disease recurs unless it demonstrates growth or persistence following chemotherapy, thus demonstrating chemoresistance (Williams et al. 1994). Radiotherapy is another option for recurrent disease. KIT targeting in dysgerminoma has not been well studied and future studies are expected. Alternatively, for patients with advanced disease or otherwise poor prognosis, supportive care alone is an option.

4.4 Ovarian Malignant Germ Cell Tumor in Pregnancy

Although a rare event, the propensity for OMGCT to present in young reproductive aged women results in them accounting for 18–26 % of all ovarian cancers recognized in pregnancy. Dysgerminoma is the most frequently encountered OMGCT in pregnancy. OMGCT diagnosed in pregnancy are usually unilateral and stage I, mirroring the typical presentation in nongravid women (Kodama et al. 2014). These tumors can sometimes be recognized in the context of a persistent adnexal mass due to markedly elevated tumor markers; however, this can sometimes be obscured by the expected presence of markers such as AFP during pregnancy.

Review of the literature indicates that, although rates of preterm birth are higher than those in the general population, the majority of these cases result in delivery of viable infants. Pregnancy preservation is in general a reasonable option. However, due to the tendency of OMGCT to disseminate rapidly, intervention should not be delayed until delivery. Surgical staging can be performed if suspicion for an ovarian malignancy is raised even during pregnancy. Although there are no randomized control trials to provide guidance, observational studies indicate that BEP is safe in pregnancy (Karimi Zarchi et al. 2008). Furthermore, advanced stage disease diagnosed during pregnancy has been identified as an independent predictor of decreased survival (Kodama et al. 2014). Therefore, although identification of a suspected OMGCT does not necessitate pregnancy termination, early intervention consistent with the standard of care is recommended if the patient desires continuation of the pregnancy.

5 Conclusion

Nonepithelial cell ovarian cancers are rare entities. Sex cord-stromal tumors and malignant germ cell tumors are the most common nonepithelial ovarian cancers. Although not encountered often, it is important to consider these tumors in differential diagnoses of adnexal masses. These tumors often, but not always, present with the sequelae of overproduction of either androgens or estrogens. It is important to diagnose these masses early, as overall prognosis is typically very good for early stage disease in all histological subtypes. Both sex cord-stromal tumors and malignant germ cell tumors of the ovary are treated with initial surgical resection. Fertility sparing surgery can be considered for both sex cord-stromal and malignant germ cell tumors of the ovary. Depending on the pathological diagnosis and disease stage, postoperative management consists of either expectant management or adjuvant chemotherapy. It is recommended that all patients with nonepithelial ovarian cancer be monitored for evidence of disease recurrence on a standardized schedule.

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Cervical Cancer: General Overview

Seiji Mabuchi, Mahiru Kawano, Yuri Matsumoto, and Tadashi Kimura

Contents

Abstract

Cervical cancer is the most common cancer affecting women in developing countries and the fourth most common type of malignancy affecting women worldwide, with almost half a million cases diagnosed each year. The median age at diagnosis of cervical cancer patients is 49 years. Persistent human papilloma virus (HPV) infection is the most important factor influencing the development of cervical cancer. According to previous research, the prevalence rate of HPV is >99 %. Cervical cancer progresses slowly from cervical intraepithelial neoplasia to invasive cancer. Thus, screening asymptomatic women with Papanicolaou cytological smears allows preinvasive disease to be diagnosed. Although widespread screening has significantly reduced the impact of cervical cancer on women in industrialized countries, such screening is not performed routinely in less developed countries, where most patients present with advanced disease and cervical cancer remains a leading cause of cancer death in women. This chapter outlines some general information that clinicians need to know in order to understand and manage uterine cervical cancer.

Keywords

Cervical cancer • HPV • Diagnosis • Clinical stage • Treatment

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1 Introduction

Cervical cancer is the most common form of cancer affecting women in developing countries and the fourth most common type of malignancy affecting women worldwide, with almost half a million cases diagnosed each year. This section outlines some general information that clinicians need to know in order to understand and manage uterine cervical cancer.

2 Epidemiology

2.1 Prevalence

Worldwide, cervical cancer is the fourth most common form of cancer affecting women, with approximately 530,000 new cases arising in 2012 and accounts for 7.5 % of all female cancer deaths. It is estimated that cervical cancer causes >270,000 deaths each year worldwide, with >85 % of them occurring in less developed regions (Torre et al. 2015).

2.2 The Role of Human Papilloma Virus and Vaccines Against It

Virtually all cases of cervical cancer are caused by specific types of human papillomavirus (HPV). There are more than 100 types of HPV, of which more than 40 can be sexually transmitted. Among these, at least 13 are considered to be high-risk cancer-causing types (Bouvard et al. 2009). Two of these high-risk types, HPV-16 and HPV-18, cause about 70 % of cervical cancers worldwide (Wheeler et al. 2009). HPV is mainly transmitted through sexual contact, and most people are infected with HPV shortly after their first sexual encounter. Despite the high prevalence of HPV, the majority of HPV infections clear up, and only a minority persist and progress to cervical intraepithelial neoplasia (CIN) or invasive cancer. The 2-year clearance rate of HPV infections is as high as 90 % (Ho et al. 1998). As our understanding of the role played by HPV infections in cervical cancer has improved, vaccines against HPV have emerged as an important cancer prevention tool. Currently, vaccines against HPV-16 and –18 have been approved for use in many countries. Such vaccines were found to be highly effective at preventing CIN as well as adenocarcinoma in situ due to HPV-16 and –18 in previously unexposed women (Ault and Group FIS 2007).

2.3 Risk Factors

The risk factors for cervical cancer are mostly associated with an increased risk of acquiring an HPV infection. They include first having sexual intercourse at a young age, having multiple sexual partners, delivering your first child at a young age, experiencing an increased number of full-term pregnancies (Berrington de González et al. 2007; Muñoz et al. 2002), and having a history of sexually-transmitted infections (Anttila et al. 2001). Oral contraceptive use appears to be associated with an increased risk of cervical cancer, especially adenocarcinoma (Appleby et al. 2007), and cigarette smoking seems to be associated with an increased risk of squamous cell carcinoma but not adenocarcinoma (Berrington de González et al. 2007). As people living with HIV/AIDS are susceptible to infection by oncogenic viruses including HPV, cervical cancer is considered to be an AIDS-defining cancer together with Kaposi's sarcoma and some types of lymphoma (Rubinstein et al. 2014).

3 Diagnosis

3.1 Clinical Manifestations

Early cervical cancer patients are frequently asymptomatic; therefore, cancer screening is important for identifying such patients. The first symptom of early cervical cancer is usually a watery or mucinous vaginal discharge, but this often goes unnoticed by the patient. The most common presenting symptom is irregular, intermenstrual, or abnormal vaginal bleeding after sexual intercourse (vaginal bleeding, after sexual intercourse). As the cervical tumor

enlarges, the bleeding episodes become heavier and more frequent. Indicators of more advanced disease include pain that seems to arise from the flank or leg (such pain is usually a secondary symptom of pelvic wall or sciatic nerve involvement); dysuria, hematuria, or rectal bleeding resulting from bladder or rectal invasion; fatigue; weight loss; loss of appetite; or a single swollen leg caused by lymphatic or venous blockade.

3.2 Diagnosis

During physical examinations, the cervix and entire vagina should be inspected and palpated to identify overt tumors or subepithelial vaginal extension. The lesion can manifest as an exophytic tumor in the exocervix, an infiltrating tumor of the endocervix, or an ulcerative tumor. Tumors that arise in the endocervical canal can result in an enlarged, indurated cervix with a smooth surface (referred to as a "barrel-shaped cervix"). Tumor size and parametrial involvement are best assessed using a rectovaginal examination. Palpation of the liver, supraclavicular lymph nodes, and groin should be used to diagnose distant metastasis. In women with visible lesions, a suspected diagnosis of cancer must be confirmed by a biopsy of the lesion. Symptomatic women without visible lesions and those who only present with abnormal cervical cytological findings should undergo a colposcopy-directed biopsy (followed by endocervical curettage) and, if necessary, diagnostic conization. Conization can also be used to determine whether conservative or radical surgery is required in cases of microinvasive cancer.

4 Staging

4.1 Clinical Staging

The most widely accepted staging system for cervical cancer is the four-stage system developed by the International Federation of Gynecologists and Obstetricians (FIGO) (Table 1) (Pecorelli 2009). The FIGO classification of cervical cancer was originally based on the results of clinical examinations. Cervical tumors are staged using the FIGO system at the time of the initial diagnosis. Thus, it is of critical importance that pelvic examinations are performed by experienced examiners. Since the revised FIGO staging system for uterine cervix was published in 2009, the FIGO Committee on Gynecologic Oncology has encouraged the use of imaging techniques for evaluating lesion size and growth. Other investigations (i.e., examinations performed under anesthesia, cystoscopy, sigmoidoscopy, or intravenous pyelography) are considered optional (Pecorelli et al. 2009).

4.2 Diagnostic Studies

4.2.1 Tumor Size and Local Spread

It remains unclear whether imaging studies can assess tumor size and local spread more accurately than clinical examinations in cervical cancer patients. However, a prospective multi-institutional study involving 208 women with early-stage cervical cancer showed that magnetic resonance imaging (MRI) is superior to computed tomography (CT) and clinical examinations for evaluating tumor size (Mitchell et al. 2006). Moreover, in a meta-analysis of 57 studies, it was suggested that MRI is superior to CT for evaluating parametrial involvement (Bipat et al. 2003).

4.2.2 Lymph Node and Distant Metastases

The FIGO staging system does not take lymph node involvement into account, but the information regarding the lymphatic spread of cervical cancer is important in determining its prognosis and the most appropriate treatment. Historically, surgery with lymphadenectomy was required to evaluate for lymph node metastasis. Currently, the options for evaluating for lymph node metastasis include lymph node dissection, imaging studies, or both. The initial evaluation of the lymph nodes is usually performed with CT to minimize costs, but positron emission tomography (PET) and PET/CT might be able to evaluate patients' lymph node status more accurately. According to a meta-analysis of 72 studies involving 5042

Table 1 2009 modification of FIGO staging for carcinoma of the cervix uteri[a]

Stage			Descriptions
Stage I			The carcinoma confined to the cervix[b]
	IA		Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm[b]
		IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
		IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
	IB		Macroscopically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA[c]
		IB1	Lesion ≤4.0 cm in greatest dimension
		IB2	Lesion >4.0 cm in greatest dimension
Stage II			Clinically visible cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
	IIA		Lesion without parametrial invasion
		IIA1	Lesion ≤4.0 cm in greatest dimension
		IIA2	Lesion >4 cm in greatest dimension
	IIB		Lesion with obvious parametrial invasion
Stage III			The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney
	IIIA		Tumor involves lower third of the vagina, with no extension to the pelvic wall
	IIIB		Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
Stage IV			The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
	IVA		Spread of the growth to adjacent organs
	IVB		Spread to distant organs

[a]Adopted and modified from the original source
[b]Extension to the corpus would be disregarded
[c]The involvement of vascular/lymphatic spaces should not change the stage allotment

women (Selman et al. 2008), the sensitivity and specificity of the abovementioned imaging modalities for detecting lymph node metastases are as follows: PET: 75 % and 98 %, respectively; MRI: 56 % and 93 %, respectively; CT: 58 % and 92 %, respectively.

5 Histology

The World Health Organization recognizes three general categories of invasive carcinoma of the cervix: squamous cell carcinoma, adenocarcinoma, and other epithelial tumors (IARC. WHO histological classification of tumors of the uterine cervix) (Table 2). Squamous cell carcinoma is the most common histological subtype, accounting for 60–70 % of invasive carcinomas. Adenocarcinoma and adenosquamous carcinoma comprise 20–25 % of all cases, and the other types account for 10–15 % of cases. However, the proportion of cervical adenocarcinoma has recently been increasing (Smith et al. 2000).

6 Spread and Metastasis

6.1 Direct Invasion

Cervical cancer principally spreads via direct local invasion of the adjacent tissues and lymphatic system and, less commonly, through blood vessels. Initially, the malignant cells penetrate the basement membrane, and then progressively infiltrate into the underlying stroma. Cervical tumors grow laterally into the paracervical and parametrial areas and can also invade the uterine cavity and vagina, before progressing into the urinary bladder and rectum.

Table 2 WHO histological classification of invasive carcinomas of the uterine cervix[a]

Histological classification			
Squamous cell carcinoma	Microinvasive squamous cell carcinoma		
	Invasive squamous cell carcinoma	Keratinizing	
		Nonkeratinizing	
		Basaloid	
		Verrucous	
		Warty	
		Papillary	
		Lymphoepithelioma-like	
		Squamotransitional	
Adenocarcinoma	Early invasive adenocarcinoma		
	Invasive adenocarcinoma	Mucinous adenocarcinoma	Endocervical
			Intestinal
			Signet-ring cell
			Minimal deviation
			Villoglandular
		Endometrioid adenocarcinoma	
		Clear cell adenocarcinoma	
		Serous adenocarcinoma	
		Mesonephric adenocarcinoma	
Other epithelial tumors		Adenosquamous carcinoma	
		Glassy cell carcinoma variant	
		Adenoid cystic carcinoma	
		Adenoid basal carcinoma	
		Neuroendocrine tumors	Carcinoid
			Atypical carcinoid
			Small cell carcinoma
			Large cell neuroendocrine carcinoma
		Undifferentiated carcinoma	

[a]Adopted and modified from the original source

6.2 Lymphatic Spread

The lymphatic spread of cervical cancer occurs relatively early, and the risk of lymph node metastasis increases with the depth of invasion. The reported incidence of lymph metastasis in each FIGO stage of cervical cancer is as follows: stage IA1: 0–0.8 %; stage IA2: 0–7.4 %; stage IB: 11.7–23.2 %; stage IIA: 10.0–26.8 %; stage IIB: 35.2–48.6 % (Buckley et al. 1996; Cosin et al. 1998; Creasman et al. 1998; Elliott et al. 2000; Hirai et al. 2003; Kasamatsu et al. 2002; Lee et al. 1989, 2006; Östör and Rome 1994; Poynor et al. 2006; van Meurs et al. 2009).

The lymphatic spread of cervical cancer usually occurs in an orderly fashion from the pelvic lymph nodes, most commonly the obturator or external iliac lymph nodes, to the common iliac lymph nodes, and then the para-aortic lymph nodes (PALN). However, cervical cancer can directly metastasize to the PALN, although this is very rare. According to a retrospective study involving 61 patients with invasive cervical cancer who displayed solitary positive lymph nodes after radical hysterectomy (RH) plus systematic lymphadenectomy, metastasis to each nodal site occurred at the following frequencies: external iliac lymph nodes: 43 %, obturator lymph nodes: 26 %, parametrial lymph nodes: 21 %, common iliac lymph nodes: 7 %, presacral lymph nodes: 1 %, and PALN: 1 % (Bader et al. 2007).

Ovarian involvement due to direct invasion is rare. Instead, it usually occurs via lymphatic spread. In a study of patients with stage IB cervical cancer, the Gynecologic Oncology Group reported that ovarian involvement was detected in 4 of 770 patients (0.5 %) with squamous cell carcinoma and 2 of 121 patients (1.7 %) with adenocarcinoma (Sutton et al. 1992).

6.3 Hematogenous Metastasis

Hematogenous metastasis can also occur in cervical cancer patients. The most common sites of hematogenous spread are the lungs, liver, and bone.

6.4 Surgical Staging of the PALN

PALN metastases are seen in 9–24 % of stage II cases, 12–38 % of stage III cases, and 13–50 % of stage IVA cases (Heller et al. 1990; Michel et al. 1998). Failure to detect metastases to the PALN can lead to suboptimal treatment and lower survival.

Pretreatment surgical staging might be beneficial as it allows adequate histological evaluations of the retrieved PALN and can lead to treatment modification in certain cases. In addition, debulking enlarged positive lymph nodes during surgical staging might be of therapeutic benefit. However, the role of surgical staging of the PALN in cervical cancer has never been investigated in a randomized study, and thus, its clinical value remains unclear.

Pretreatment surgical staging is associated with an increased postoperative morbidity rate and treatment delays. According to a previous report, the mean complications rate of surgical PALN staging procedures is 9 % (range: 4–24 %) (Fine et al. 1995; Hughes et al. 1980). Retrospective studies have suggested that a retroperitoneal approach, laparoscopic surgery, and robotic surgery are all associated with lower rates of postoperative complications compared with an intraperitoneal approach (Smits et al. 2014). Thus, these less invasive approaches might be recommended for surgical PALN staging procedures.

It has been suggested that PET (with or without CT) is the most accurate imaging modality for assessing extrapelvic disease in cervical cancer (PET, extrapelvic disease in cervical cancer). It was reported that PET produces a high true-positive rate (50–100 %), indicating that surgical staging might not be necessary if uptake is detected in the para-aortic region. Nevertheless, false-negative results in the para-aortic region have been recorded in 12–22 % of patients, indicating the weakness of PET for detecting small metastases (Gouy et al. 2012). The comparative advantages of the surgical staging of the PALN over clinical assessments based on imaging technologies, such as PET, in terms of the complications rate and survival need to be investigated in large randomized controlled trials.

7 Treatment

The treatment of invasive cervical cancer involves the management of both the primary lesion and any metastatic disease. For early-stage cervical

Table 3 Classification of radical hysterectomy according to Piver, Rutledge, and Smith[a]

Class	Description
Class I: Extrafascial hysterectomy	
	Deflection and retraction of the ureters without dissection of the ureteral bed
	Uterine artery is laterouterine sectioned and ligated
	Uterosacral ligament and cardinal ligament are not removed
	No vaginal portion is excised
Class II: Modified radical hysterectomy (Wertheim)	
	Ureters are freed from the paracervical position but are not resected from the pubovesical ligament
	Uterine arteries are ligated just medial to the ureter
	Uterosacral ligaments are resected midway between the uterus and their sacral attachments
	Medial half of the cardinal ligaments are removed
	Upper one-third of the vagina is removed
	Elective pelvic lymphadenectomy
Class III: Classical radical hysterectomy (Meigs')	
	Complete dissection of the ureter from the pubovesical ligament to entry into the bladder except for a small lateral part of the pubovesical ligament
	Uterine vessels are ligated at the origin of the internal iliac artery
	Uterosacral ligaments are resected at their sacral attachments
	Cardinal ligaments resected as close to the pelvic wall
	Upper half of the vagina is removed
	Routine pelvic lymphadenectomy
Class IV: More radical than class III in three aspects	
	(i) Complete dissection of the ureter from the pubovesical ligament
	(ii) The superior vesicle artery is sacrificed
	(iii) Upper three-fourth of the vagina is removed
Class V: More radical than class IV	
	Involved portions of the distal ureter or bladder are excised

[a]Adopted and modified from the original source

cancer, both surgery and radiotherapy can be used to treat the primary lesion. In contrast, radiotherapy is the only curative treatment for advanced disease. The choice of treatment should be based on the extent of the cervical cancer, the patient's age and general health, and the complications of the patient.

The advantages of a primary surgical approach are as follows: First, it facilitates accurate tumor staging. Second, it allows ovarian function to be preserved in premenopausal patients. Third, it makes it possible to remove bulky lymph nodes that cannot be cured with external beam radiotherapy. The main advantage of radiotherapy is that it is applicable to almost all patients, whereas radical surgery cannot be used to treat patients with medically inoperable disease.

7.1 Surgical Treatment

7.1.1 Classification of Radical Hysterectomy

The first case series in which RH was used to treat cervical cancer was reported by Ernst Wertheim in 1912 and was followed by a study by Okabayashi (Okabayashi 1921; Werheim 1912). Today, RH is commonly categorized according to the amount of the parametrium that is resected.

In 1974, Piver et al. published a classification of RH (Piver et al. 1974) (Table 3). This classification is still widely used, although two newer classifications have been proposed to overcome the ambiguities of the original one (Mota et al. 2008; Querleu and Morrow 2008).

7.1.2 Morbidities Associated with Radical Surgery for Cervical Cancer

RH is associated with various postoperative morbidities, including bladder dysfunction, sexual dysfunction, and colorectal motility disorders. Accidental damage to the pelvic autonomic nerves during surgery is considered to be a major cause of such morbidities.

According to previous studies, bladder dysfunction including incomplete bladder emptying and a need to strain to micturate occur in 16–40 % of patients (Bergmark et al. 2006; Kenter et al. 1989), 9–18 % of patients suffer constipation (Bergmark et al. 2006; Sood et al. 2002), fecal or flatal incontinence is seen in 33 % of patients (Kenter et al. 1989), fistulas develop in 1–6.7 % of patients (Kenter et al. 1989; Lee et al. 1989), lymphedema occurs in 3–19 % of patients (Bergmark et al. 2006; Pieterse et al. 2006), and 19–36 % of patients experience sexual dysfunction (Bergmark et al. 2006; Pieterse et al. 2006).

7.1.3 Nerve-Sparing Radical Hysterectomy

In an effort to reduce the postoperative morbidity rate, nerve-sparing RH (NSRH), which protects the pelvic nerves that can be damaged during RH, was developed by Japanese gynecologists, and the procedure has been improved over the last 20 years (Fujii et al. 2007). A recent meta-analysis suggested that although NSRH exhibited a significantly longer operating time than RH, NSRH results in greater postoperative recovery of pelvic organ function and a lower postoperative morbidity rate than RH (Long et al. 2014).

7.2 Radiotherapy

Radiotherapy is an extremely useful treatment for cervical cancer because the uterine cervix is able to tolerate high-radiation doses. Radiotherapy can be used to treat all stages of cervical cancer; however, as the volume of the primary cervical lesion increases, the likelihood of sterilizing it with radiation decreases. Thus, for patients with bulky tumors or locally advanced disease, the risk of locoregional recurrence remains significant, leading to poor survival.

Pelvic external beam radiotherapy involving a dose of 50 Gy combined with brachytherapy is the gold standard treatment for cervical cancer. During such treatment, initial external beam radiotherapy involving the delivery of 40–45 Gy to the whole pelvis is often necessary to induce tumor shrinkage and facilitate the intracavitary installation of the radiation source. In cases involving gross disease in the parametrial or pelvic lymph nodes, an external beam boost to 60–65 Gy can be administered.

8 Prognosis

The survival outcomes of cervical cancer patients according to the FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer are shown in Table 4 (Quinn et al. 2006).

9 Conclusion

Cervical cancer remains a significant health problem for women worldwide. However, the introduction of widespread screening and/or HPV vaccines would significantly reduce its impact. Moreover, the use of multidisciplinary approaches to the treatment of cervical cancer has led to marked improvements in patient outcomes.

Table 4 Prognosis of cervical cancer according to FIGO stage[a]

	Overall survival (%) at	
FIGO stage	3 year	5 year
IA1	98.3	97.5
IA2	95.2	94.8
IB1	92.6	89.1
IB2	81.7	75.7
IIA	81.5	73.4
IIB	73.0	65.8
IIIA	54.0	39.7
IIIB	51.0	41.5
IVA	28.3	22.0
IVB	16.4	9.3

[a]Adopted and modified from the original source

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Sentinel Node Mapping in Vulva Cancer

Mamoru Kakuda, Eiji Kobayashi, Kiyoshi Yoshino, and Tadashi Kimura

Contents

Abstract

The treatment of early-stage vulvar cancer previously included a complete inguinofemoral lymph node dissection (IFLD). However, IFLD is associated with a substantially high probability of postoperative complications: up to two-thirds of patients who have IFLD performed experience wound infection or breakdown, formation of lymphocytes, or long-term lymphedema. For this reason, lymphatic mapping and sentinel lymph node biopsy (SLNB) for early-stage vulvar cancer have been studied. Compared to IFLD, SLNB has significantly fewer complications and is becoming a more common practice in treatment for selected patients with early-stage vulvar cancer. From our literature review, we discuss SLNB as part of a standard treatment for patients with early-stage vulvar cancer, and we provide future considerations for its use in the management of vulvar cancer.

Keywords

Vulvar cancer • Sentinel nodes • Inguinofemoral lymph node dissection • Early stage • Complication

1 Introduction

Sentinel lymph node (SLN) identification and lymphatic mapping for vulvar cancer have its origins in cancers of other sites. In 1960, Gould

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et al. first proposed the concept of a "sentinel node" for head and neck cancer in their description of the key node which was identified at the junction of the anterior and posterior facial vein (Gould et al. 1960). In the field of gynecologic cancers, DiSaia et al. first utilized the superficial inguinal lymph nodes as the "sentinel nodes" in the treatment of vulvar cancer to help them identify patients who would not benefit from a more morbidity-causing complete IFLD (DiSaia et al. 1979). In the 1990s, Morton et al. described what is now the new procedure lymphatic mapping in the treatment of melanoma, in which blue dye was used to identify the primary lymphatic drainage basin (Morton et al. 1992).

The premise of SLN biopsy (SNLB) is that tumor cells from the primary lesion will first migrate "downstream" in the lymphatic flow to one or a few key lymph nodes, prior to disseminating to other regional lymph nodes. These key lymph nodes can be identified by using either a vital blue dye (isosulfan blue/methylene blue), a radiocolloid, or indocyanine green (ICG). Key to the utilization of this technique is confidence that identification of the SLN accurately predicts the status of the remaining lymph nodes.

Surgery still remains the primary care for early-stage vulvar cancer, but in the past two decades, the standard treatment has made a transition from radical dissection to minimally invasive surgery. Primarily, the surgical treatment of early-stage vulvar cancer includes a complete inguinofemoral lymph node dissection (IFLD). However, IFLD is associated with a significantly high probability of postoperative complications; up to two-thirds of patients who have had extensive dissection of inguinal lymph node performed experienced wound infection or breakdown and lymphocyst formation or long-term lymphedema after surgery (Stehman et al. 1992; Gaarenstroom et al. 2003; Rouzier et al. 2003; Kirby et al. 2005). Because of this high morbidity, and since vulvar cancer is an excellent target for the SLN concept, the tumor is easy to inject with blue dye or radiocolloid. Because the lymph drainage is predictably to one or both of the groins, lymphatic mapping and SLNB for early-stage vulvar cancer have been widely studied as a possible alternative procedure to current IFLD procedures. As a result of those studies, SLNB has now become more common in the treatment for selected patients with early-stage vulvar cancer.

2 Patient Selection for SLNB Versus IFLD

As mentioned above, IFLD is associated with a high morbidity rate, including a 20–40 % risk of wound complications and a 30–70 % risk of lower extremity lymphedema. In addition, fewer than one-third of early-stage vulvar cancer patients have lymph node metastasis, which means that the routine application of IFLD exposes a large number of patients to potentially preventable surgical complications (Sedlis et al. 1987).

The most effective way to minimize morbidity in patients where surgical treatment of vulvar cancer is performed is to minimize damage of the lymphatic tracts by removing fewer lymph nodes. The benefits of dissecting fewer nodes, however, must outweigh the risk of failing to remove actual metastatic lymph nodes in the inguinofemoral region, as inguinal and pelvic recurrence of vulvar cancer is associated with a 27 % 5-year survival rate (Maggino et al. 2000).

Two large trials have evaluated whether SLNB accurately detected positive lymph node and whether SLNB reduced morbidity as compared with IFLD in patients with early-stage vulvar cancer (Van der Zee et al. 2008; Levenback et al. 2012). The GROINSS-V study was an observational study of 276 patients with squamous cell cancer of the vulva, with T1/T2 (<4 cm) and no lymph node metastases detected on SLNB (Van der Zee et al. 2008). Study investigators found that patients with multifocal disease had a higher recurrence rate after SLNB (11.8 %) compared with patients with unifocal disease (2.3 %). The false-negative rate for SLNB of multifocal disease was 5.9 % (4.6 % for patients with unifocal disease), and the false-negative predictive value was 2.9 %. This study suggested it was less common for surgical morbidity in patients who underwent only removal of SLN, compared with patients with a metastatic sentinel node who subsequently

underwent IFLD. Wound breakdown, cellulitis, lymphedema, and recurrent erysipelas are also significantly less after SLNB compared to IFLD. A follow-up survey sent to patients after the GROINSS-V study found that no difference in overall quality of life was observed between the two procedure groups and that the major difference found was the increase in complaints of lower extremity lymphedema after IFLD (Oonk et al. 2009).

The Gynecologic Oncology Group (GOG) Protocol 173 was a multi-institutional observational study of 452 patients with early-stage vulvar cancer (Levenback et al. 2012). All patients underwent intraoperative lymphatic mapping and SLNB, followed by IFLD. The overall false-negative rate for SLNB was 3.7 %. However, the false-negative rate for SLNB was much lower in women with tumors smaller than 4 cm than in women with tumors 4–6 cm (2.0 % vs. 7.4 %). In addition, the location of the tumor was another important factor found in a systematic review (Hassanzade et al. 2013). For lesions which were within 2 cm of the midline, the detection rate was considerably lower compared with more lateral lesions greater than 2 cm from the midline plane (73 % vs. 95 %).

From this evidence, we suggest that patients with early-stage vulvar cancer, with primary tumors that are unifocal and smaller than 4 cm and where the lesion(s) are located more than 2 cm from the midline, can be assured preoperatively that, if the SLNB is negative, the risk of a recurrence of the inguinal lesion is less than 3 %. Given the cumulative results from these studies, we feel confident that the SLNB can be offered to patients carefully selected by skilled gynecologic oncologists. In clinical practices where vulvar cancer is rarely encountered and experience of the surgeon with the disease is negligible, referral to a high-volume center and a more experienced surgeon is recommended.

3 Drainage Tracer

In the GOG Protocol 173, the false-negative rates for SLNs identified by dye and radiocolloid, dye alone, and radiocolloid alone were 1.6 %, 2.0 %, and 7.8 %, respectively (Levenback et al. 2012). A meta-analysis of 29 studies of SLNB for vulvar cancer found that the pooled SLN detection rates were 94.0 % for 99mTc, 68.7 % for blue dye alone, and 97.7 % for combined 99mTc and blue dye (Meads et al. 2014). These results demonstrate evidence that a combination of radiocolloid and blue dye is the most sensitive for detecting SLN. Because of the direct visualization of the lymphatic mapping for vulvar cancer provided by using blue dye, using the combination of radiocolloid and blue dye may also improve the learning curve for the SLNB procedure.

In recent years, near-infrared (NIR) fluorescence imaging has been introduced in lymphatic mapping and SLNB for vulvar cancer. The NIR technique has the potential for far more accurate and real-time intraoperative SLN mapping. A meta-analysis of SLNB with NIR fluorescence imaging in vulvar cancer has reported a good outcome, with a high detection rate of inguinal lymph node metastasis (91.4 %) and a considerably higher negative predictive value (100 %) (Handgraaf et al. 2014). However, the penetration capacity of NIR fluorescence is limited to approximately 8 mm. The use of radiotracers therefore remains indispensable, since it allows preoperative scintigraphy and intraoperative identification of deep SLN in the groin. Further studies will therefore be needed to compare the effectiveness of ICG with radiocolloid injection versus the traditional combination approach of blue dye and radiotracer.

4 Ultrastaging

Ultrastaging is the term used to describe intense histologic examination of the SLN samples. Ultrastaging is unrealistic in the daily practice setting and is thus rarely performed because it is an onerous task to examine the, on average, ten

lymph nodes per groin removed by conventional IFLD. In contrast, ultrastaging is amenably performed on the 1–2 lymph nodes per groin obtained by SLNB. The combination of hematoxylin-eosin (H&E) and cytokeratin immunohistochemical (IHC) staining of paraffin-embedded SLN tissue that is sectioned every 0.4 to 0.5 mm intervals (as contrasted with the 2 to 3 mm section intervals used for traditional lymph node evaluations) has led to the identification of micrometastases in SLN otherwise thought to be void of lymph node metastasis by conventional pathologic examination. IHC staining should thus be added to H&E staining for more accurate identification of micrometastases.

In GOG Protocol 173, 23 % of all SLN were detected to be positive by immunohistochemistry when the routine H&E staining did not reveal metastatic disease (Levenback et al. 2012). In the GROINSS-V study, the authors reported that, of 135 positive SLN in 403 patients, 80 (59 %) were detected with routine sectioning and H&E staining, 19 (14 %) were detected by ultrastage sectioning using H&E staining, and a further 36 (27 %) positive SLN were detected by ultrastaging with immunohistochemical staining. The risk of a non-SLN metastases was higher when the SLN was found positive by routine histological assessment than by ultrastaging (27.1 % vs. 5.4 %) (Oonk et al. 2010). In patients with SLN metastasis identified by ultrastaging, the 5-year overall survival rate was higher than in patients with SLN metastasis identified by routine pathological examination (89 % vs. 65 %).

Without examination of the lymph nodes removed by SLNB or full IFLD by the same pathological evaluations, it will be difficult to confirm the true value of the detection of micrometastases by ultrastaging of SLN. A better consensus on the standards for pathological evaluations and the need for ultrastaging is required.

5 Recurrence Rate

Recurrence of vulvar cancer in the groin is usually a fatal event, making it an important outcome measurement for this patient population. IFLD patients were historically divided into two groups: superficial and complete resection. Complete resection was used to describe an inguinofemoral lymphadenectomy combined with removal of the deep femoral lymph nodes, while superficial resection was used to describe procedures without an attempt to remove the deep femoral lymph nodes. Using complete resection, the lowest reported rate of groin recurrence following IFLD was about 1 %. However, rates of surgical morbidity, especially wound breakdown and lymphedema, were excessively high (Stehman et al. 1992).

In the case of superficial resection, inguinal recurrence rates of 5–7 % were seen and were considered less acceptable compared with historical controls (Robison et al. 2014). For SLNB, the groin recurrence rate was expected to be less than 3 %. For well-selected patients with vulvar cancer, this result seems to be an acceptable compromise that minimizes surgical morbidity. Of course, for a tailored treatment in a clinical situation, the informed consent procedure for SLNB for vulvar cancer needs to include as a possible option a full IFLD. For patients with a 1 cm squamous cell carcinoma with less than 2 mm of stromal invasion, the risk of recurrence is approximately 1 %, if the SLN is negative for metastasis. In contrast, for patients with a 4 cm or larger vulvar cancer, accompanied deep stromal invasion, the risk of recurrence is significantly higher, even if the SLN is negative for metastasis.

6 Survival Rate

Regardless of the type of lymphadenectomy, an inguinal recurrence of vulvar cancer worsens the survival rate (Martinez-Palones et al. 2006; Terada et al. 2006; Moore et al. 2008; Van der Zee et al. 2008; Oonk et al. 2010). Achimas-Cadariu et al. reported that the median overall survival period was 61.2 months but was only 16.2 months for patients who experienced a relapse (Achimas-Cadariu et al. 2009).

The GROINSS-V study is the largest investigation to date into the disease-specific survival rate among patients with no detected metastases

by SLN (Van der Zee et al. 2008). At a median follow-up time of 35 months, the 3-year disease-specific survival rate among patients with unifocal vulvar disease and a negative SLN was 97.0 %. The 3-year disease-specific survival for patients with sentinel node metastases larger than 2 mm was lower than for those with metastases 2 mm or smaller tumors (69.5 % vs. 94.4 %) (Oonk et al. 2010).

7 Complications

Surgical complications for vulvar cancer include wound infection, wound breakdown, lymphocele, and long-term lymphedema. However, wound complications have decreased dramatically since the implementation of the "separate groin incision" technique (Wills and Obermair 2013). A recent systematic review regarding complication rates of IFLD reported that lymphedema occurs in 14–48 % of patients after groin dissection, lymphocele formation in 7–40 %, wound infection in 21–39 %, and wound breakdown in 17–39 % (Wills and Obermair 2013). Estimates for complications following an SLNB and IFLD were reported in the GROINSS-V study. For SLNB and IFLD, the wound breakdown rate was 11.7 % vs. 34 %, cellulitis was 4.5 % vs. 21.3 %, and lymphedema was 1.9 % vs. 25.2 %, respectively (Van der Zee et al. 2008). The results of the Levenback et al. (2012) validation study (GOG Protocol 173) demonstrated similar results to the GROINSS-V study (Van der Zee et al. 2008).

8 Quality of Life

IFLD, particularly when it is followed by radiation or chemoradiation, can aggravate the patient's quality of life (QOL). One study (62 patients) investigating QOL with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) found few differences between SLNB and IFLD; only the score regarding financial difficulties was significantly worse in the IFLD group. For the FACT-V questionnaire, there were significantly worse results for the scales concerning contentment functional, lymphedema, and complaints and stockings symptoms (Oonk et al. 2009).

Novackova et al. observed increased fatigue and more impaired lymphedema in patients with vulvar cancer after IFLD, compared with those after SLNB (Novackova et al. 2015). Forner et al. found that IFLD had a negative influence on the patients' sexual function (Forner et al. 2015). Additional studies are required to see how SLNB versus IFLD impact QOL in patients with vulvar cancer.

9 Cost-Effectiveness of SLNB

Erickson et al. compared the costs of SLNB with IFLD (Erickson et al. 2014). Their analysis concluded that SLNB is the most cost-effective strategy for the management of patients with early-stage vulvar cancer due to lower treatment costs and lower costs due to complications. Although there are additional costs associated with SLNB, including tracer injections, intraoperative mapping, imaging, and ultrastaging, these costs are offset by a shorter hospitalization. While both management strategies have similar disease-free survival estimates, the difference in treatment costs is approximately $4000 more for the IFLD per patient than for SLNB.

McCann et al. also reported a similar cost-effective analysis of SLNB and IFLD (McCann et al. 2015). Their analysis discovered that SLNB was less costly than IFLD ($13,449 vs. $14,261) and more effective for quality of life (4.16 quality-adjusted life years (QALYs) versus 4.00 QALYs). In this study, variations in the rate of positive SLNB and probability of lymphedema over clinically reasonable ranges did not alter the results. In their study, the increase in lymphedema associated with IFLD played a major role in the differences the costs between SLNB and IFLD.

SLNB is associated with shorter surgical time, fewer postoperative complications, and lower costs associated with postoperative complications. The incidence of lymphedema following

IFLD are reported to be much higher, as high as 67 % in one prospective study (Carlson et al. 2008). Among patients where only SLNB was performed, the morbidity rate was 1.9 % (Van der Zee et al. 2008).

10 Learning Curve for Conducting SLNB

Vulvar cancer is a rare condition and the SLNB for it is a technically challenging procedure for surgeons. Acquiring experience in identifying the SLN accurately in patients with vulvar cancer is a very significant challenge. Schutter et al. describe the SLNB procedure as a complex interaction process between clinicians, specialists in nuclear medicine, and pathologists. So, if this interaction is ever inadequate, SLNB of vulvar cancer could have lethal consequences (Schutter and van der Sijde 2014). Given the strong potential for variations in operator skill in identifying SLN, an expert panel convened in 2008 recommended that a gynecologic oncologist performed at least ten consecutive cases with successful SLN identifications and no false-negative results before performing stand-alone SLNB without lymphadenectomy (Levenback et al. 2009).

While surgeons participating in the GOG Protocol 173 were not required to have a specific level of experience in conducting SLNB, surgeons participating in the GOG Protocol 270 were (GROINSS-V II study). Studies often define the first ten cases as part of the learning curve, after which SLNB without IFLD could be performed (Hampl et al. 2008; Van der Zee et al. 2008). Levenback et al. calculated that the rate of failure to identify an SLN was worse during the first 2 years of the study (16 % in the first 2 years and then 7 % for subsequent years) (Levenback et al. 2012).

Klapdor et al. reported that single-photon emission computed tomography (SPECT/CT) leads to higher SLN identification compared to lymphoscintigraphy in vulvar cancer (Klapdor et al. 2015). Due to its higher spatial resolution and three-dimensional anatomical localization of SLN, the number of cases required to become a skilled surgeon in SLNB for vulvar cancer may be reduced by the use of preoperative SPECT/CT and by observing other surgical oncologists as they perform SLNB for breast cancer or melanoma (Chapman et al. 2016).

11 Conclusion

The development of SLNB in treatment for vulvar cancer has involved an unprecedented level of cooperation among investigators in Europe and the United States. SLNB is recommended for patients with early-stage vulvar cancer with primary tumors that are unifocal and smaller than 4 cm with clinically non-suspicious lymph nodes of metastasis in the groin, provided there is specific infrastructure with well-skilled surgeons. Some recommendations for appropriate techniques and procedures are also provided. Further recommendations on the management of patients with SLN metastasis are currently pending until the results are available from the GOG Protocol 270, which will incorporate the next phase of the GROINSS-V study (GROINSS-V II study). The purpose of this latter study is to investigate whether the dissection of SLN followed by chemotherapy and/or radiation is effective in managing early-stage vulvar cancer.

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Workup and Management of Polycystic Ovary Syndrome

Gillian Mackay and Alexandra Regens

Contents

Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in females. It is a heterogeneous condition that frequently manifests in adolescence. Signs and symptoms include various combinations of hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. The etiology of PCOS is still largely unknown, although genetic and environmental factors including insulin resistance and obesity have been implicated. Diagnosis is based upon fulfillment of the 2003 Rotterdam criteria, which require two of three cardinal features – hyperandrogenism, oligomenorrhea or amenorrhea, and polycystic ovaries on ultrasound. Careful history and physical exam are critical first steps in evaluation. Initial evaluation also involves documenting the presence of hyperandrogenism and ruling out other diagnoses. Ultrasound imaging should be considered as part of the initial evaluation and monitoring but is not necessary for all patients. Treatment remains largely empirical with an emphasis on managing the risks of metabolic sequelae, such as diabetes and cardiovascular disease. Other features, such as hyperandrogenism and menstrual irregularity, are managed symptomatically. This chapter will discuss the clinical features of PCOS with a focus on diagnostic workup and management.

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Polycystic ovaries • PCOS • Anovulatory cycles • Amenorrhea • Hyperandrogenism • Ovulatory dysfunction • Metabolic syndrome • Rotterdam criteria

1 Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in females. It is a heterogeneous condition that frequently manifests in adolescence. Various combinations of hyperandrogenism, ovulatory dysfunction, and polycystic ovaries characterize PCOS. The etiology of PCOS is still largely unknown, although genetic and environmental factors including insulin resistance and obesity have been implicated. Treatment remains largely symptomatic and empirical with an emphasis on managing the risks of metabolic sequelae, such as diabetes and cardiovascular disease. This chapter will discuss the clinical features of PCOS with a focus on diagnostic workup and management.

2 Epidemiology

PCOS affects approximately five million women of reproductive age in the United States (Johnson et al. 2012). The exact prevalence within this population varies depending on which diagnostic criteria are applied. It is widely cited as ranging from 6 % to 10 % (Azziz 2015; ACOG Practice Bulletin No. 108 2009). However, when using the broader Rotterdam criteria, it could actually be as high as 15 % (Fauser et al. 2012).

Populations at increased risk include women with anovulatory cycles, obesity, insulin resistance, diabetes mellitus, premature adrenarche, an affected first-degree relative, and antiepileptic drug use (Azziz 2015). Some preliminary studies have shown a possible increased risk in Hispanic women as compared to Caucasians and African Americans (Azziz 2015). Most data, however, has shown strikingly similar prevalence of PCOS across various ethnic groups with no single ethnicity having definitively been identified as high risk Azziz et al. 2011.

3 Etiology

PCOS is a syndrome with multiple etiologies that are not fully understood. It is a multifactorial genetic trait with influence from both heritable and nonheritable factors. Inherited gene variants may include those regulating the secretion and action of gonadotropins and insulin, weight and energy regulation, and androgen biosynthesis and action (Johnson et al. 2012; Azziz 2015).

Epigenetic factors such as obesity and insulin resistance have been implicated in the pathogenesis for some patients. Increased body mass index is associated with increased serum testosterone and decreased sex hormone-binding globulin (Barbieri 2015). Increased circulating insulin leads to the release of insulin-like growth factor 1 (IGF-1) from the liver. IGF-1 causes the ovaries to release higher levels of testosterone. These abnormal levels of insulin, IGF-1, and testosterone act on the ovary, preventing the maturation of follicles and subsequently resulting in the accumulation of multiple small ovarian follicles (Johnson 2014). However, only 50–70 % of women with PCOS demonstrate clinically measurable insulin resistance and only about 60–70 % are obese (Azziz 2015; Fauser et al. 2012); therefore these factors alone cannot explain all cases.

4 Diagnostic Criteria

PCOS has no universally accepted definition, and several expert groups have convened to put forth diagnostic criteria over the years. These criteria vary in their inclusion of the three main characteristics of PCOS – hyperandrogenism, ovulatory dysfunction, and polycystic ovaries – as being necessary for diagnosis. A 2012 National Institute of Health (NIH) workshop on PCOS has suggested the use of the 2003 Rotterdam criteria (Johnson et al. 2012; Barbieri and Ehrmann 2015a). The 1990 NIH and 2006 Androgen Excess Society diagnostic criteria remain

Table 1 Diagnostic criteria of PCOS

1990 National Institute of Health (NIH)	2006 Androgen Excess Society (AES)	2003 Rotterdam criteria
Requires the presence of **both** of the following: Hyperandrogenism Oligomenorrhea or amenorrhea	Requires the presence of hyperandrogenism	Requires the presence of **two** of the following: Hyperandrogenism Oligomenorrhea or amenorrhea Polycystic ovaries on ultrasound
Does not include polycystic ovaries on ultrasound	Requires the presence of **one** of the following: Oligomenorrhea or amenorrhea Polycystic ovaries on ultrasound	

clinically relevant and are also included for reference. All three sets of diagnostic criteria are summarized in Table 1.

The 1990 National Institute of Health (NIH) diagnostic criteria require the presence of both hyperandrogenism and oligomenorrhea or amenorrhea (ACOG Practice Bulletin No. 108 2009; Rosenfield 2015). These criteria account for the majority of PCOS patients (Rosenfield 2015). The presence of polycystic ovaries on ultrasound is not included (ACOG Practice Bulletin No. 108 2009; Rosenfield 2015), making this characteristic neither necessary nor sufficient for diagnosis under the NIH criteria (Rosenfield 2015).

The 2006 Androgen Excess Society (AES) diagnostic criteria make hyperandrogenism necessary for diagnosis, requiring clinically or biochemically evident hyperandrogenism along with either of the two remaining characteristics (ACOG Practice Bulletin No. 108 2009; Rosenfield 2015).

The European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine convened to develop the 2003 Rotterdam criteria (Rosenfield 2015). These criteria require the presence of any two of the three PCOS characteristics (ACOG Practice Bulletin No. 108 2009; Rosenfield 2015). Hyperandrogenism may be evident clinically or biochemically. The Rotterdam criteria are, therefore, the most broad of the proposed criteria (Rosenfield 2015). As mentioned, the 2012 NIH workshop recommends utilizing the Rotterdam criteria due to their broad, inclusionary nature (Johnson et al. 2012).

All diagnostic criteria recommend excluding conditions that can mimic PCOS before finalizing the diagnosis. This includes other disorders that cause anovulation or hyperandrogenism, such as adult-onset congenital adrenal hyperplasia, hyperprolactinemia, androgen-secreting neoplasms, thyroid disease, Cushing syndrome, acromegaly, primary hypothalamic amenorrhea, primary ovarian failure, and genetic defects in insulin action (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015a).

Diagnosing PCOS in adolescence presents a unique challenge, as some characteristic features, such as acne and anovulatory menstrual cycles, are common and nonspecific in this population. It has been suggested that all three components of the Rotterdam criteria should be present to diagnose PCOS in adolescents. It is also suggested that at least 2 years of oligomenorrhea or amenorrhea after menarche (or primary amenorrhea at 16 years old) and biochemically evident hyperandrogenemia be present to help prevent overdiagnosis (Fauser et al. 2012).

5 Evaluation

The Rotterdam criteria allow for diagnosis based upon a careful history and physical exam (Barbieri and Ehrmann 2015a). The history should include detailed menstrual history, presence of signs or symptoms consistent with hyperandrogenism, and medications. The patient should be asked about family history of diabetes and cardiovascular disease (ACOG Practice Bulletin No. 108 2009). PCOS typically manifests as irregular menses in adolescence. The diagnosis is less likely in women with new onset oligomenorrhea after 30 years of age (Barbieri

and Ehrmann 2015a). Physical exam should include measurements of blood pressure, body mass index, and waist circumference. Signs of hyperandrogenism and insulin resistance, such as acne, hirsutism, androgenic alopecia, and acanthosis nigricans, should be documented (ACOG Practice Bulletin No. 108 2009).

The main components of the laboratory workup are documenting biochemical hyperandrogenemia and ruling out other possible diagnoses. Androgens can be measured with total testosterone and sex hormone-binding globulin or bioavailable and free testosterone. Other causes of hyperandrogenism should be excluded by measuring thyroid-stimulating hormone (thyroid disorder), prolactin (hyperprolactinemia), and 17-hydroxyprogesterone (nonclassical congenital adrenal hyperplasia). Rapid progression of new onset hirsutism or signs of virilization such as deeping of the voice or clitoromegally indicate that serum dehydroepiandrosterone sulfate (DHEA-S) should be measured to rule out presence of an androgen-secreting tumor (Barbieri and Ehrmann 2015a). Consider screening for Cushing syndrome if stigmata such as hypertension, supraclavicular fat pads, purple striae, or proximal muscle weakness are present on exam (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015a).

PCOS is associated with increased prevalence of a metabolic syndrome including type 2 diabetes, dyslipidemia, and coronary heart disease, as well as mood disorders and sleep apnea. Screening for their presence is recommended and can be performed as part of the initial workup. Evaluation should include a 2-h oral glucose tolerance test and measurement of fasting lipid profile (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015a). Consider measuring fasting insulin levels in women who are young, have signs of severe insulin resistance or hyperandrogenism, or are undergoing ovulation induction (ACOG Practice Bulletin No. 108 2009). Mood disorders can be screened for using validated tools such as the PHQ-9 for depression and GAD-7 for anxiety (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015a; Hussain et al. 2015). Women should be asked about excessive daytime sleepiness and other signs of sleep apnea, and if suggestive of the diagnosis, referred to a sleep medicine specialist (Barbieri and Ehrmann 2015a).

The role of ultrasound in PCOS has evolved over time. Under the Rotterdam criteria, a patient with oligomenorrhea and hyperandrogenism may be diagnosed without documentation of polycystic ovaries on ultrasound. If ultrasound is to be performed for diagnosis, transvaginal approach is recommended over transabdominal (Barbieri and Ehrmann 2015a). The Rotterdam ultrasound criteria are fulfilled by the presence of 12 or more follicles measuring 2–9 mm in diameter in one or both ovaries or increased ovarian volume greater than 10 cm^3 (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015a). Ultrasound evaluation also has a role outside of diagnostic purposes. Transvaginal ultrasound is recommended for patients who are ready to conceive to monitor ovulatory status (Barbieri and Ehrmann 2015a).

PCOS is associated with a 2.7-fold increased risk of developing endometrial cancer. Endometrial surveillance by transvaginal ultrasound or endometrial biopsy should be considered based upon clinical suspicion. Indications for surveillance include women with PCOS who have thickened endometrium, prolonged amenorrhea, unopposed estrogen exposure, or abnormal uterine bleeding (Barbieri and Ehrmann 2015a; Dumesic and Lobo 2013).

6 Clinical Manifestations and Management

Up to 95 % of women with PCOS experience irregular menses. Amenorrheic women tend to have a more severe overall phenotype, with greater hyperandrogenism and higher antral follicle counts, as compared to oligomenorrheic women or those with regular cycles. Despite these irregularities, spontaneous ovulation may still occur and has been reported in up to 32 % of menstrual cycles. Menstrual cycles tend to become more regular later in life as women approach menopause (Fauser et al. 2012). Obesity

perpetuates reproductive abnormalities in women with PCOS. Even modest weight reduction with loss of 5–10 % of body weight has been shown to lower circulating levels of androgens and can result in spontaneous resumption of menses (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015c). In women not desiring pregnancy, combination low-dose hormonal contraceptives are recommended as the first-line treatment to achieve cycle control (ACOG Practice Bulletin No. 108 2009; Fauser et al. 2012; Barbieri and Ehrmann 2015c; Mendoza et al. 2014). Metformin is an acceptable second-line therapy, restoring ovulatory cycles in 30–50 % of patients (Barbieri and Ehrmann 2015c).

Women with PCOS may be subfertile (Fauser et al. 2012). It is important to optimize the patient's health prior to conception. Preconception counseling should focus on the importance of weight loss and exercise, smoking cessation, reducing alcohol consumption, and folic acid supplementation (ACOG Practice Bulletin No. 108 2009; Fauser et al. 2012). Again, even modest weight loss is associated with improved pregnancy rates (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015c). First-line therapy for ovulation induction is clomiphene citrate (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015c). Live birth rates following 6 months of clomiphene therapy range from 20 % to 40 %. Most pregnancies will occur within the first six ovulatory cycles, but there may be some benefit to a longer course (ACOG Practice Bulletin No. 108 2009). For patients who fail clomiphene, exogenous low-dose gonadotropins or laparoscopic ovarian surgery may be used (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015c; Donesky 2015). Insulin-sensitizing agents, preferably metformin due to its favorable safety profile, have not been supported as first-line therapy for ovulation induction but can improve ovulation rate when used in conjunction with clomiphene, especially in obese patients (ACOG Practice Bulletin No. 108 2009; Johnson 2014). When women with PCOS do become pregnant, they are at an increased risk for adverse pregnancy outcomes. PCOS is associated with increased rates of gestational diabetes, gestational hypertension, and newborn morbidity and mortality (Fauser et al. 2012).

Hyperandrogenism can manifest as hirsutism, acne, or alopecia. About 70 % of women with PCOS experience hirsutism. Acne and alopecia are less prevalent (Fauser et al. 2012). Overall, treatment of hirsutism tends to be palliative rather than curative and there is no agreed-upon first-line treatment (ACOG Practice Bulletin No. 108 2009). Due to the slow rate at which terminal hair turns over, treatment requires at least 6 months before expecting a response (Fauser et al. 2012). Weight loss decreases hirsutism by decreasing circulating androgen levels (ACOG Practice Bulletin No. 108 2009). Pharmacologic treatment of hirsutism is focused on decreasing free testosterone and limiting the activity of androgens in the hair follicles. Oral contraceptive pills increase levels of sex hormone-binding globulin levels and, therefore, decrease free testosterone. They are often prescribed in combination with an antiandrogen, such as spironolactone, flutamide, or finasteride. It is important that antiandrogens are only used with effective contraception due to their potential teratogenic effects. Topical eflornithine hydrochloride can be used to decrease development of new unwanted facial hair growth. Hair may also be removed physically through electrolysis or laser treatments (ACOG Practice Bulletin No. 108 2009; Fauser et al. 2012). For severe acne, isotretinoin may be effective. There is currently no effective treatment for androgenic alopecia (Fauser et al. 2012).

In the United States, about 60–70 % of women with PCOS are obese (Fauser et al. 2012). Diet and lifestyle changes must be emphasized as modest weight loss as little as 5 % of initial weight can improve reproductive and metabolic abnormalities. When these interventions fail, improvement in ovarian function has been seen with the use of pharmacologic agents, such as orlistat and sibutramine (ACOG Practice Bulletin No. 108 2009). Morbidly obese women with PCOS may consider gastric bypass surgery (ACOG Practice Bulletin No. 108 2009; Barbieri

and Ehrmann 2015c). It is not known whether weight loss is beneficial for normal weight women with PCOS (ACOG Practice Bulletin No. 108 2009).

Not only is there a high prevalence of obesity in this population, but they also tend to have upper-body fat distribution with greater abdominal or visceral adiposity. This puts these patients at increased risk for insulin resistance, impaired glucose tolerance, gestational diabetes, and type 2 diabetes (Fauser et al. 2012). Women with PCOS have a two to fivefold increased risk of diabetes compared to control populations with up to 40 % demonstrating glucose intolerance. Metabolic syndrome, consisting of hypertension, increased waist circumference, elevated fasting glucose, reduced high-density lipoprotein cholesterol, and elevated triglycerides, is common. One large study found that 33 % of PCOS patients have metabolic syndrome (ACOG Practice Bulletin No. 108 2009). Diet and lifestyle changes should be implemented first line in women at risk for type 2 diabetes or metabolic syndrome. In women with frank diabetes or in those with impaired glucose tolerance who do not respond adequately to lifestyle modifications, treatment with metformin should be initiated (ACOG Practice Bulletin No. 108 2009; Fauser et al. 2012). Insulin-sensitizing agents such as thiazolidinediones and glucagon-like peptide-1 analogues should be used with caution in women of reproductive age (Fauser et al. 2012). These drugs are classified as FDA pregnancy category C, and their use may result in resumption of ovulation, increasing the risk of pregnancy.

Women with PCOS are three times more likely to have the classic cardiovascular disease risk markers (impaired glucose tolerance, metabolic syndrome, type 2 diabetes, dyslipidemia) than women without PCOS. This is exaggerated in obese patients. Patients should undergo periodic cardiovascular risk assessment, including measurement of body mass index, psychosocial stress screening, blood pressure, glucose, lipid profile, waist circumference, physical activity, nutrition counseling, and smoking assessment (ACOG Practice Bulletin No. 108 2009; Fauser et al. 2012).

Women with PCOS may have an increased risk of endometrial, ovarian, and breast cancer although there is limited data to support these conclusions. Disruption of the normal reproductive physiology increases the risk. The most documented association is an increased risk of endometrial cancer, for which there appears to be a two to sevenfold increase risk in PCOS patients (Fauser et al. 2012; Dumesic and Lobo 2013). Endometrial cancer in this population usually has a good prognosis. At this time, there is not a widely accepted modality to screen for endometrial cancer, and decision to assess should be based on clinical factors. Suspicion should be raised in the setting of abnormal uterine bleeding or endometrial hyperplasia, on imaging and correlated with the patient's age (Fauser et al. 2012). Endometrial protection can be provided through the use of low-dose combined hormonal contraceptives. Alternative therapy includes intermittent or continuous progestin therapy or a progestin-releasing intrauterine device (ACOG Practice Bulletin No. 108 2009; Barbieri and Ehrmann 2015c).

7 Conclusion

PCOS typically presents in adolescence and is characterized by various combinations of hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. PCOS affects approximately 6–15 % of women of reproductive age in the United States. Populations at increased risk include women with anovulatory cycles, obesity, insulin resistance, diabetes mellitus, premature adrenarche, an affected first-degree relative, and antiepileptic drug use. PCOS arises from both heritable and nonheritable factors. Epigenetic factors such as obesity and insulin resistance have been implicated in the pathogenesis for some patients.

The 2012 NIH workshop recommends utilizing the Rotterdam criteria for diagnosis. Diagnosis under these criteria requires the presence of any two of the three PCOS characteristics, hyperandrogenism, oligomenorrhea or amenorrhea, and polycystic ovaries. Evaluation of the PCOS patient should include careful history and

physical exam, documentation of hyperandrogenism, and exclusion of other differential diagnoses. Patients should also be screened for cardiometabolic sequelae and other comorbid conditions. Treatment of PCOS is largely symptomatic, but lifestyle changes through diet modification and exercise should take a central role.

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Management of Recurrent Pregnancy Loss

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Contents

Abstract

Recurrent pregnancy loss (RPL) defined as two pregnancies diagnosed on ultrasound or histopathologic examination or any three consecutive pregnancy losses. Approximately 2 % of reproductive aged women experience RPL in contrast to the 15 % of women who experience sporadic losses. Etiologies are varied and research continues to further understanding of the unknown. Management of recurrent pregnancy loss depends largely on the etiology, keeping in mind that approximately 50 % of cases will be unexplained. Improved outcomes are achieved when this condition is managed by a specialist, who can provide psychological support throughout diagnosis and management. Briefly, when karyotype abnormalities are encountered, the couple will need genetic counseling and may be offered prenatal genetic screening or even assisted reproductive techniques to largely ensure a euploid fetus. Anatomic abnormalities of the uterus are often managed surgically. When antiphospholipid antibody syndrome is encountered, treatment with aspirin and heparin has been shown to improve outcomes. Treatment of overt thyroid disease, diabetes mellitus, or hyperprolactinemia is warranted to normalize hormone values. Anticoagulation may be warranted for inherited conditions; however testing and treatment of acquired conditions are not advised. Given that a large percentage of cases are unexplained, treatment options for this subset

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have also been proposed including lifestyle modifications, or as last resort oocyte donation or gestational surrogacy.

Keywords
Recurrent pregnancy loss • Recurrent miscarriage • Habitual aborter • Unexplained pregnancy loss • Idiopathic pregnancy loss

1 Introduction

Recurrent pregnancy loss (RPL) can be a challenging and complicated problem, defined as two or more failed clinical pregnancies diagnosed ultrasonographically or histopathologically or any three consecutive pregnancy losses. This problem is encountered by approximately 2 % of reproductive aged women, in contrast to 15 % of reproductive aged women who experience sporadic **miscarriage**. **RPL** is complex because of the fact that an etiology is often not encountered, in approximately 50 % of cases, and because of the fact that the problem is psychologically very taxing for couples (Li et al. 2002). **RPL**, defined as three or more **miscarriages**, is thought to affect 1 % of reproductive aged couples (Stirrat 1990; Salat-Baroux 1988). This condition is further complicated by the lack of randomized clinical data, and most recommendations are based on meta-analysis, observational studies, and expert opinions (Practice Committee of the American Society for Reproductive Medicine 2012). However, patients can be reassured that live birth rates after normal and abnormal diagnostic testing are 71 % and 77 %, respectively (Harger et al. 1983). It has been reported that patients have improved outcomes when managed by a specialist with experience in the treatment of RPL.

2 Causes and Management of Recurrent Pregnancy Loss

2.1 Karyotypic Abnormalities

When chromosomal abnormalities are discovered in one or both parents, it is essential that comprehensive genetic counseling be offered to the patient. The reasons for this are twofold, one to understand the abnormalities and the rates of abnormal gametes and risk for future loss events as well as to understand the rate of transmission to future generations (Laurino et al. 2005).

Unfortunately, when products of conception are evaluated, the majority have sporadic chromosomal abnormalities. Balanced reciprocal translocations in one or both parents make up approximately 2–5 % of RPL cases, and genetic counseling is strongly encouraged to identify breakpoints, which can help couples determine their future risks and chances for success. This data, as well as the fact that RPL is approximately six times higher in first cousins, supports the suggestion that RPL may be associated with nonrandom genetic errors (Christiansen et al. 1990).

One option for these couples as well as those with RPL is embryo evaluation with preimplantation genetic screening (PGS); however, some couples opt for gamete or embryo donation. This information may be of particular importance considering that fetal chromosomal abnormalities are found in >70 % of products of conception in women greater than 35 years of age (Marquard et al. 2010).

2.2 Other Genetic Causes

A variety of other genetic causes including single or multiple gene defects or polymorphisms have also been associated with RPL. These include methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms (Chen et al. 2016). Other etiologies include skewed X chromosome inactivation and Y chromosome microdeletion in the male partner (Agarwal et al. 2015).

2.3 Uterine Abnormalities

When uterine abnormalities are encountered, which can include congenital or mullerian abnormalities, adhesive disease, or submucosal myomata, these are surgically resected with improved pregnancy rates (Mollo et al. 2009;

Tomazevic et al. 2010). Various techniques have been employed to restore normal anatomy including hysteroscopy, laparoscopic and open depending on the lesion encountered. The use of prophylactic cerclage is controversial in patients receiving uterine reconstruction for a mullerian anomaly.

2.4 Immunologic Factors

Some preliminary data suggests that in addition to immunologic disease entities, paternal antigens in the embryo may trigger a rejection response. Others postulate that abnormal expressions of normal signaling mediators such as cytokines or integrins may play a role (Saito et al. 2016).

2.4.1 Antiphospholipid Syndrome

Testing for antiphospholipid antibody syndrome (APAS) includes laboratory detection of high levels of anticardiolipin, lupus anticoagulant, or anti-β-2 glycoprotein-1 antibodies on two separate occasions in addition to the clinical criteria of vascular thrombosis of a deep vessel or unexplained death of a morphologically normal fetus >10 weeks, or premature delivery <34 weeks secondary to preeclampsia, eclampsia, or placental insufficiency, or three or more **unexplained losses** <10 weeks.

Treatment depends on the individual clinical scenario, but typically involves the use of heparin or low molecular weight heparin (LMWH) to prevent venous thromboembolic events and/or a combination of low-dose aspirin and heparin or LMWH to prevent arterial events. Therapy can begin either with conception or some groups report conception attempt for patient with history of early losses.

2.4.2 Celiac Disease

Data has suggested that untreated celiac disease is associated with infertility and pregnancy loss. This data, although not always consistent, reminds us to optimize a woman's heath ensuring that all medical conditions are treated prior to attempting pregnancy.

2.5 Endocrine Dysfunction

Patients may present with endocrine abnormalities including diabetes mellitus, thyroid disease, or hyperprolactinemia. Overt endocrine dysfunction requires prompt treatment and normalization of the underlying condition, ideally prior to conception.

2.5.1 Thyroid Dysfunction

In addition to the correction of overt thyroid disease, euthyroid patients with thyroid peroxidase antibodies appear to benefit from low-dose levothyroxine supplementation. Limited data suggests that benefits may include decreased miscarriage and preterm delivery rates (Negro et al. 2006).

2.5.2 Hyperprolactinemia

Elevated prolactin levels have been associated with increased miscarriage rate, and treatment with dopamine agonists appears to decrease rates of adverse outcomes. High prolactin levels have been suggested to cause or potentially contribute to a luteal phase defect. Treatment may include either bromocriptine or cabergoline depending on the side effect panels and cost to patients (Hirahara et al. 1998). It is also usually recommended that treatment be continued into pregnancy.

2.5.3 Luteal Phase Defect

Luteal phase abnormality was previously considered to play a role in the disruption of early pregnancies; however there is no strong evidence to suggest that exogenous progesterone supplementation prevents early miscarriage, leading to in 2015 a statement from the American Society for Reproductive Medicine, stating no need for exogenous progesterone after a pregnancy has been established. However, it has been demonstrated that progesterone supplementation is very important in assisted reproductive cycles as high steroid secretion for multiple corpora lutea negatively feeds back on the hypothalamic-pituitary axis causing decreased LH secretion and premature luteolysis (Pluchino et al. 2014).

2.6 Polycystic Ovarian Syndrome

Previous literature has shown that miscarriage rates are higher in patients with polycystic ovarian syndrome as compared with the general population. Mechanisms for this are postulated to include elevated luteinizing hormone, testosterone, or insulin resistance. Therefore, therapies should focus on normalization of hormone and insulin/glucose levels. Prior research has suggested that the use of metformin may decrease the rates of pregnancy loss; however, larger studies have failed to confirm these findings (Okon et al. 1998). Some studies suggest that a subgroup of PCOS patients with insulin resistance and obesity may benefit from anticoagulation therapy (Chakraborty et al. 2013).

2.7 Infectious/Microbial

In the past a variety of infectious agents such as *Listeria monocytogenes*, *Toxoplasma gondii*, *cytomegalovirus*, and primary genital herpes have been found to be associated with sporadic pregnancy loss however not with RPL. More recently, however, CMV has been correlated with RPL rates, and it is unclear whether the underlying etiology is any exposure to the virus or a reactivation or recurrence is responsible for adverse outcomes (Sherkat et al. 2014). Other studies have more closely examined products of conception for infections such as *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis* as well as *human papillomavirus* (HPV) and only found HPV to be more prevalent and of uncertain significance (Matovina et al. 2004).

2.8 Unexplained

As previously mentioned, in nearly the majority of patients with RPL, no etiology is found. Many patients question the role that lifestyle choices such as tobacco, alcohol, exercise, and diet play in RPL. No data clearly suggests definitive improvement with these changes. Therefore, recommendations should be based to optimize overall health.

Progesterone supplementation has long been prescribed for a variety of situations involving assisted reproductive technologies and infertility treatments. Data from meta-analysis suggests improved outcomes in patients with RPL; however given concerns and limitations, governing regulatory bodies do not recommend the use of progesterone after a pregnancy has been established (Practice Committee of the American Society for Reproductive Medicine 2015).

A variety of therapies have been tested and found to be ineffective, or the efficacy has not been proven.

The use of aspirin and/or heparin or LMWH in the absence of the diagnosis of antiphospholipid antibody syndrome.

Glucocorticoid use has not found to be effective.

There are currently no recommendations to test for inherited thrombotic disease in the evaluation of RPL.

Currently, no immunologic treatments are recommended for RPL patients.

Given the relatively good success rates of patients with RPL, PGS should not be an initial option for these patients as advised by the major organization guidelines (Thornhill et al. 2005; Practice Committee of the American Society for Reproductive Medicine and Practice Committee of the Society for Assisted Reproductive Technology 2006).

Interestingly, several studies have suggested that adequate psychological support for patients suffering from **unexplained RPL** significantly improved outcomes. Treatments included specific antenatal counseling and psychological support techniques and being managed by dedicated pregnancy loss providers (Clifford et al. 1997).

2.9 Miscellaneous

Some literature has noted that poor egg quality alone may be the cause of recurrent pregnancy loss, but further investigation is needed (Remohi

Table 1 Summarizing RPL

Categories of RPL	Percentage	Specific etiologies	Management
Anatomic	22	Congenital/mullerian anomalies Leiomyomata Polyps Intrauterine adhesions Abnormal endometrial receptivity	Surgical management of surgical abnormality Endometrial receptivity testing
Immunologic	25	APAS Cytokine/integrin factor	Anticoagulation therapy with aspirin and heparin
Endocrine	20	Diabetes mellitus Polycystic ovarian syndrome Thyroid dysfunction Hyperprolactinemia	Treatment of underlying condition
Infectious/ microbial	6	Infectious etiologies mostly responsible for sporadic not recurrent pregnancy loss	
Genetic	3	Aneuploidy Chromosomal rearrangement	Testing of products of conception, possible embryo biopsy
Unknown	40		

et al. 1996). The oocyte may not be the only gamete implicated in RPL, as a recent meta-analysis noted that DNA fragmentation in sperm was statistically significantly related to miscarriage and recommended utilizing sperm selection techniques to improve outcomes (Robinson et al. 2012).

Timing of implantation has been the focus of some researchers as they question the adage that the window of implantation is constant in all women. New data suggests that the timing of transfer may need to be individualized, and this has resulted in increased implantation and pregnancy success in the setting of RPL with euploid embryos. Endometrial receptivity testing based on these findings is being developed for clinical use (Ruiz-Alonso et al. 2014).

Integrins are now being studied in various tissues as biomarkers for a variety of both physiologic and disease processes. Beta3 integrin has been studied as a marker of implantation, and it has been shown that in patients with RPL, the expression of this integrin is significantly decreased. Reasons for this remain unclear; however the use of endometrial receptivity testing may overcome these issues or educate patients and physicians to move in other directions such as surrogacy or uterine transplantation (Germeyer et al. 2014). Table summarizing percentages, causes and management of various causes of RPL (Table 1).

3 Conclusion

RPL is a complex problem, which can be devastating to the patients experiencing this condition. Management, performed by a specialist, should focus on psychological support while underlying etiologies are diagnosed and treated. Patients should be assured that most do go on to have live births.

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Hyperandrogenism: Acne and Hirsutism

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Abstract

Hyperandrogenism is a common pathology in women, with the main physical manifestations including hirsutism and acne. Etiologies include polycystic ovarian syndrome (PCOS), idiopathic hirsutism, classical and nonclassical congenital adrenal hyperplasia (CAH), ovarian and adrenal tumors, Cushing's disease, and certain medications. The severity of the hirsutism will vary among patients, but treatment should be administered to those who desire it, even if their hirsutism is not severe. Treatment methods include weight reduction, hair removal, oral contraceptive pills, and antiandrogen medications including spironolactone, finasteride, cyproterone acetate, flutamide, and eflornithine. Treatments for acne include topical retinoids, topical antimicrobials (benzoyl peroxide), topical antibiotics (erythromycin, clindamycin, sulfacetamide, dapsone), or oral isotretinoin.

Keywords

Hyperandrogenism • Polycystic ovarian syndrome • Hirsutism • Virilization • Acne

1 Introduction

Hyperandrogenism is a medical condition resulting from excess androgens circulating throughout the female body. The most common physical manifestations include both hirsutism, defined as excessive male-patterned hair growth, and acne. Hirsutism affects between 5 % and10 % of women of reproductive age. Hirsutism is often the primary or only sign of an underlying hyperandrogen disorder, with polycystic ovarian syndrome (PCOS) being the most common (Barbieri and Ehrmann 2013a). More serious causes of hirsutism can include rare androgen-secreting adrenal tumors, which will be discussed later in this chapter.

While hyperandrogenism is a spectrum of a disorder in terms of severity, a patient may only be mildly affected but yet still be undergoing significant psychological distress and requesting treatment. This chapter will discuss the pathogenesis, evaluation, and treatment of women who have hyperandrogenism disorders.

2 Pathogenesis

2.1 Gonadotropins

The vast majority of patients with hirsutism will also experience anovulation, and the most common cause of this is PCOS. Anovulation is associated with abnormal pulsatility of gonadotropin-releasing hormone (GnRH) from the hypothalamus. PCOS commonly has elevated luteinizing hormone (LH) with lower or normal follicle-stimulating hormone (FSH). It is theorized that decreased or lack of overall progesterone (P4) production from the postovulatory corpus luteum results in decreased negative feedback on the hypothalamus (Lebovic et al. 2013a). Increased LH activity leads to higher ovarian androgen production, suppressing SHBG, leading to elevated free androgens. The androgens are converted to estrone in peripheral tissue, leading to decreased FSH levels. The lower levels of FSH lead to follicular arrest and lead to anovulation which is commonly seen in hyperandrogenism.

2.2 Hyperinsulinemia

Hyperinsulinemia and hyperandrogenism are commonly associated pathologies. Hyperinsulinemia leads to decreased insulin-like growth factor-binding protein (IGFBP-I) concentrations that can lead to increased *free* insulin-like growth factor I (IGF-I). Both insulin and IGF-I suppress hepatic SHBG production, leading to increased free androgens. Increased insulin can also stimulate androgen production directly or stimulates LH secretion from the pituitary (Dorn et al. 2004). Serine phosphorylation of the insulin receptor can occur in PCOS and insulin resistance conditions. Serine phosphorylation leads to reduced glucose transportation and stimulation of 17-hydroxylase which increases adrenal and ovarian androgen production. There are also syndromes involving severe insulin resistance that result from genetic defects in the insulin receptor, antibody production to insulin receptors, and syndromes of lipoatrophy and lipodystrophy (Barbieri and Ehrmann 2013b).

2.3 Androgen Excess

Both increased insulin production and LH secretion lead to hyperplasia of ovarian theca cells, resulting in increased levels of testosterone (T), androstenedione (which can be either ovarian or adrenal in origin), dehydroepiandrosterone (DHEA), 17-hydroxyprogesterone (17-OHP), and estrone (E1) levels. Estradiol (E2) production is often unchanged (Lebovic et al. 2013a). Decreased sex hormone-binding globulin (SHBG) levels from the liver also lead to increased *free* levels of androgens and estrogen (Lebovic et al. 2013a). Elevated levels of androstenedione are converted by aromatase to estrone within peripheral adipose cells (Barbieri and Ehrmann 2013b), which is a leading reason why women with hyperandrogenism are at an increased risk for endometrial carcinoma due to chronic increased estrogen exposure to the endometrial lining. In response to the increased level of estrogen, FSH is suppressed by negative feedback, and ovarian follicles subsequently undergo degeneration. Once the follicles degenerate, fluid accumulates and forms subcortical ovarian cysts, which causes the overall volume of the ovaries to increase (Goljan and Sloka 2007).

The adrenal glands are another source of androgen production. Patients that have nonclassical congenital adrenal hyperplasia (NCAH) can have a genetic defect in 21-hydroxylase (CYP21B) or 3-beta-hydroxysteroid dehydrogenase (3bHSD) genes. Both genetic enzyme defects and androgen-producing adrenal tumors result in increased adrenal dehydroepiandrosterone sulfate (DHEA-S) (Lebovic et al. 2013a).

2.4 Hirsutism

Androgen excess in women leads to an unwanted increase in hair growth in androgen-sensitive sites such as the upper lip, sideburns, periumbilical region, mid chest, mid thighs, upper back, and buttocks. In response to these increased androgen levels, hair follicle size, coarseness, and diameter are increased, and the time the hair spends in the growth phase (anagen phase) is increased (Barbieri and Ehrmann 2013b). Testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase within a hair follicle, which then results in short and soft vellus hairs to become coarse terminal hair (Schorge and Williams 2008a).

2.5 Alopecia

Thinning of the hair and/or temporal balding is associated with DHT levels within hair follicles. Hair loss is a slow and progressive course in female androgenic alopecia (Schorge and Williams 2008a).

2.6 Acne

Although acne vulgaris is a common adolescent finding, acne that is persistent into young adulthood or acne with a late onset should raise suspicion that the patient might have PCOS (Schorge and Williams 2008a). Similar to the hair follicle, testosterone is converted to DHT by 5-alpha-reductase within the sebaceous glands. Androgen excess stimulates androgen receptors within pilosebaceous units. This in turn increases sebum production and proliferation of *Propionibacterium acnes* leading to inflammation, blockage of hair follicles, and comedone formation (Schorge and Williams 2008a). As will be discussed later in the chapter, treatment of acne focuses on reducing colonization of *P. acnes*, inflammation, sebum production, and scarring.

2.7 Sex Hormone-Binding Globulin (SHBG)

SHBG is a glycoprotein produced by the liver that binds most sex steroids. Estrogen increases the synthesis of SHBG, but SHBG has a higher binding affinity for testosterone than estrogen. Conversely, insulin, androgens, obesity, and hypothyroidism lead to lower levels of SHBG (Goljan and Sloka 2007). Decreased SHBG levels result in lower amount of bound androgens to SHBG, and therefore increased levels of free and unbound androgens remain available to bind to

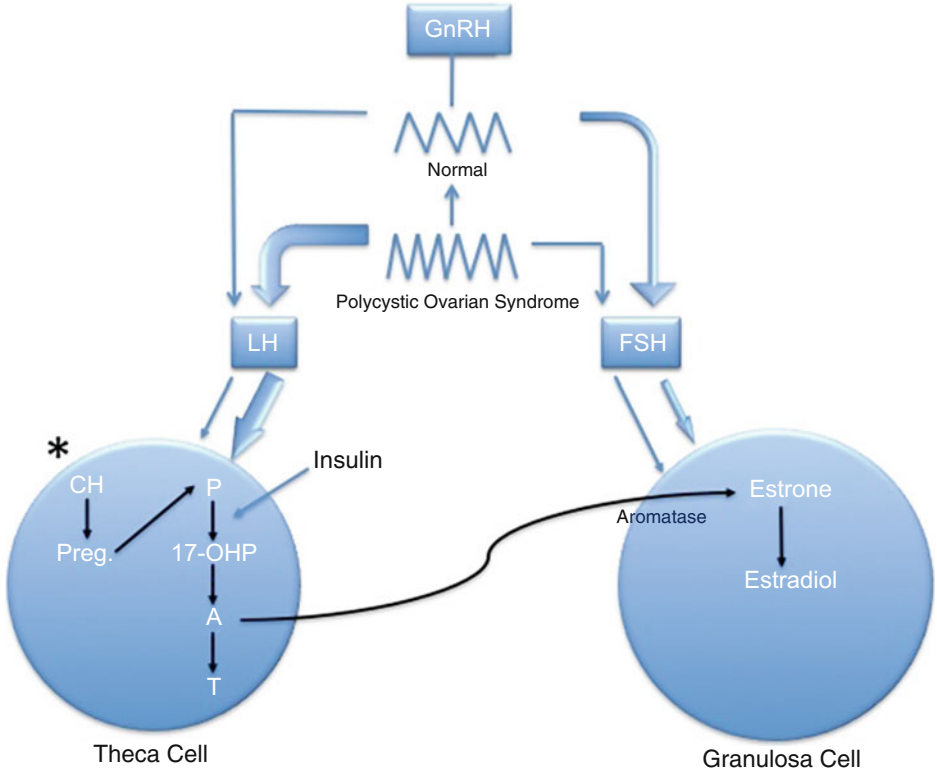

Fig. 1 Mechanism of action regarding the etiology of hyperandrogenism/hyperestrogenism in patients with PCOS. This diagram compares both normal and abnormal pathways. *GnRH* gonadotropin-releasing hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *CH* cholesterol, *Preg* pregnenolone, *P* progesterone, *17-OHP* 17-hydroxyprogesterone, *A* androstenedione, *T* testosterone (Schorge and Williams 2008a)

end-organ receptors leading to hyperandrogenism (Lebovic et al. 2013a; Schorge and Williams 2008a). For example, women with PCOS may have normal total T levels but elevated free unbound T (Schorge and Williams 2008a).

Figure 1 shows the mechanisms of action regarding the etiology of hyperandrogenism/hyperestrogenism. The enzymatic pathway of testosterone synthesis within the theca cell is shown in Fig. 2.

3 Etiologies of Hirsutisms and Acne

3.1 Etiologies

Etiologies of hirsutism include PCOS, idiopathic hirsutism, and congenital adrenal hyperplasia. Other uncommon etiologies include ovarian tumors, adrenal tumors, Cushing's disease, hyperthecosis, severe insulin resistance syndromes, and iatrogenic drug exposure.

3.2 PCOS

PCOS is the most common underlying etiology of hirsutism, resulting in 75–80 % of patients with signs and symptoms (Barbieri and Ehrmann 2013a). The diagnosis of PCOS is usually made in the early reproductive time frame when androgen production is increased by both the ovaries and the adrenal glands (puberty and adrenarche, respectively). According to the Rotterdam criteria, these patients must have two of the three following symptoms to be diagnosed with PCOS: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic

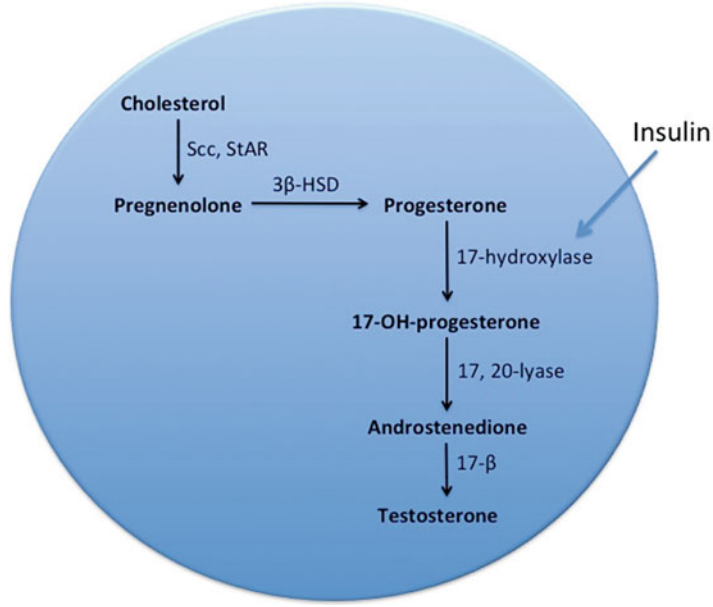

Fig. 2 A breakdown and larger view of the enzymatic pathway of testosterone synthesis within the theca cell. *Scc* side-chain cleavage enzyme, *StAR* steroidogenic acute regulatory protein, *3β-HSD* 3β-hydroxysteroid dehydrogenase (Schorge and Williams 2008a). Insulin resistances lead to serine phosphorylation of the insulin receptor, increased 17-hydroxylase activity, and increased adrenal and ovarian androgen production

ovaries (12 or more follicles in one or both ovaries or ≥10 cc volume) (Rotterdam 2004). In addition to hirsutism, these patients will also need to be treated and screened for underlying comorbidities such as obesity, obstructive sleep apnea, dyslipidemia, hypertension, glucose intolerance, type 2 diabetes mellitus, and metabolic syndrome. As PCOS is a diagnosis of exclusion, other etiologies of hirsutism should first be ruled out such as idiopathic hirsutism (hirsutism with normal cycles and normal androgen levels), congenital adrenal hyperplasia, Cushing's syndrome, and hyperprolactinemia. If a patient has symptoms similar to PCOS but complains of recent onset of hirsutism (usually within 1 year), has onset in the third decade of life or later instead of near puberty, or has signs of virilization (frontal/temporal balding, acne, clitoromegaly, increased muscle mass, or voice deepening), an androgen-secreting tumor should be ruled out (Barbieri and Ehrmann 2013a).

It is uncertain if hyperthecosis is a distinct diagnosis by itself or is a more severe spectrum disorder of PCOS. However, it is theorized that hyperthecosis is a nonmalignant ovarian disorder in which testosterone is significantly elevated by luteinized theca cells. Its gradual presentation is similar to that of PCOS, but these patients will have frank virilization in addition to hirsutism (Barbieri and Ehrmann 2013b).

3.3 Idiopathic Hirsutism

This diagnosis is given to women who have hirsutism but without menstrual irregularities and have normal serum androgen levels (Azziz et al. 2000). However, this diagnosis is not very common, and it has been reported that over 90 % of women diagnosed with idiopathic hirsutism meet the Rotterdam PCOS diagnostic criteria of hyperandrogenism (hirsutism) and polycystic ovaries noted on transvaginal ultrasound (Adams et al. 1986).

3.4 Congenital Adrenal Hyperplasia (CAH)

CAH presents in two different forms: classical CAH and nonclassical CAH. Both disorders involve excess androgen production. Classical CAH is usually recognized at birth or in early infancy as these patients have ambiguous genitalia from virilization and adrenal crisis. However, the nonclassical form of CAH usually entails

patients presenting in the peripubertal time frame complaining of hirsutism and oligo- or amenorrhea (Barbieri and Ehrmann 2013b). Nonclassical CAH is almost always due to 21-hydroxylase (P450c21) deficiency. This leads to a shift in the standard adrenal steroid synthesis pattern resulting in increased production of both 17-OHP and androstenedione. 17-OHP is a substrate for 21-hydroxylase and is an androgen precursor to androstenedione (Barbieri and Ehrmann 2013b).

3.5 Ovarian Tumors

Androgen-secreting tumors constitute only 5 % of all ovarian tumors. The most common androgen-producing ovarian tumors include Sertoli-Leydig cell tumors (androblastoma, arrhenoblastoma), granulosa-theca cell tumors (stromal cell), and hilus cell tumors (Barbieri and Ehrmann 2013b). Similar to PCOS, women with ovarian tumors present with signs and symptoms of hyperandrogenism later in life. However, the onset is much more rapid than the gradual onset seen in patients with PCOS (Barbieri and Ehrmann 2013b).

3.6 Adrenal Tumors

Although a rare cause of hirsutism, adrenal adenomas/carcinomas should still be part of the differential diagnosis. Adrenal tumors can secrete androgens and/or cortisol. Therefore, these women can present with signs and symptoms of hirsutism and Cushing's syndrome (Barbieri and Ehrmann 2013b).

3.7 Cushing's Syndrome

Cushing's syndrome refers to excessive physiologic exposure of cortisol from the adrenal glands or other sources. Cushing's disease results specifically from corticotroph adenomas producing excessive ACTH, resulting in adrenal over activity. Excessive levels of both cortisol and adrenal androgens lead to hirsutism in addition to the other classic features of Cushing's syndrome: central obesity, dark purple striae, and the characteristic "buffalo hump" of fat deposition of the posterior aspect of the neck (Barbieri and Ehrmann 2013b). It is of important to note that although most of all women that have Cushing's syndrome will have hirsutism, Cushing's syndrome is rare and is the pathologic diagnosis in an extremely small percentage of women with hirsutism (Barbieri and Ehrmann 2013b).

3.8 Drugs

Drugs commonly associated with hirsutism include exogenous testosterone, danazol (commonly used in the past as a treatment for endometriosis), metoclopramide, methyldopa, progestins, and reserpine (Schorge and Williams 2008b).

4 Evaluation

It is important to keep in mind that despite the severity of hirsutism, the presence of hirsutism in the female patient can cause severe psychological stress and insecurities in which the patient will desire prompt treatment. Therefore, the treatment of hirsutism relies on identifying the etiology and requires a thorough evaluation. Most of these patients will also have an underlying endocrine disorder that should be identified to help specifically address treatment modalities, although 75–80 % will have PCOS as their underlying cause of hirsutism (Barbieri and Ehrmann 2013a).

Hirsutism is not to be confused with two other excessive hair growth manifestations including lanugo and hypertrichosis. Lanugo is soft and vellus (short, fine, and light colored) hair that is not darkly pigmented and covers the entire body, such as that found in an infant. This hair growth is not androgen dependent. Hypertrichosis is also excessive androgen-independent hair growth in nonsexual areas that is also vellus. Hypertrichosis can be caused by systemic disorders such as anorexia nervosa, hypothyroidism, dermatomyositis, and porphyria or medications including

phenytoin, penicillamine antibiotics, diazoxide, minoxidil, or cyclosporine (Barbieri and Ehrmann 2013a). Danazol is also a medication that can lead to hirsutism that was commonly used in the past for the treatment of endometriosis secondary to its androgenic suppression of FSH and LH (Barbieri and Ehrmann 2013a).

4.1 History

Obtaining an accurate and thorough menstrual history can help determine the etiology of hyperandrogenism. This history should include menarche onset, cycle frequency and duration, and previous use of oral contraception or hormonal contraception usage. Nearly all women with hyperandrogenism will have irregular menses or amenorrhea (Barbieri and Ehrmann 2013a). However, women who have had menses regulated by oral contraceptives throughout their reproductive years will not be aware of an underlying menstrual disorder. These symptoms usually present upon attempting conception, and their menstrual irregularities are unmasked upon discontinuation of their contraceptives.

The clinician should also note the ethnicity of the patient. Patients with an Asian or Native American background typically have little body hair, while a patient with a Mediterranean background with slightly dark upper lip hair may be normal hair growth (Barbieri and Ehrmann 2013a). Therefore, if Asian or Native American patients have even a scant amount of male-patterned hair growth, further testing may be warranted. Women of Ashkenazi Jewish descent with a family history of irregular menses and hirsutism may indicate the presence of nonclassical congenital adrenal hyperplasia (Speiser 2001).

It is also important to note the family history of the patient: "Is there a history of menstrual irregularities in your family? Hirsutism? Infertility? Obesity? Early onset cardiovascular disease?" Obese women have irregular menses due to increased circulating androgen levels, which can of course worsen hirsutism. Subsequently, menstrual irregularities are worsened with increased levels of hyperandrogenism.

4.2 Physical Examination

Although hirsutism can present as a spectrum disorder, visualization of androgen-dependent terminal hair on the lip, chin, chest, abdomen, and back is easily recognized. The most common way of quantifying hair growth in hirsute women is the Ferriman-Gallwey score, which grades nine androgen-sensitive sites from 0 to 4, and scores above 8 are considered abnormal in Caucasian and African American women (8–15, mild; 16–25, moderate; and >25, severe). This score is widely used, but it should be noted that it is not a perfect scoring system. Most women who present with hirsutism have been shaving/waxing/plucking prior to presentation, and scores vary between ethnicities (i.e., an elevated score in a Caucasian woman may be normal of a woman from India.), and agreement among different physicians is not consistent. However, it is important to recognize that no matter the score, treatment should be based on how the patient perceives the severity of her own hair growth (Barbieri and Ehrmann 2013a).

Other etiologies of hirsutism must be ruled out before making the most common diagnosis of PCOS. Therefore, physical manifestations of Cushing's syndrome such as dark abdominal striae, thin skin, or bruising must be carefully evaluated. Additionally, a waist-hip ratio >0.85 is congruent with central/truncal obesity and is significantly related to insulin insensitivity (Barbieri 2013). However, although an elevated BMI is not necessarily related to insulin insensitivity, 50 % of women with PCOS do have a BMI within the obese range [1, 13]. In the event of moderate to high androgen excess, symptoms of virilization are often present such as severe acne, deepening of the voice, clitoromegaly, frontal balding, and increased muscle mass (Barbieri and Ehrmann 2013a). A pelvic examination should also be conducted to rule out mass lesions indicative of an androgen-secreting tumor (Barbieri and Ehrmann 2013a).

4.3 Diagnostic Studies

After a thorough history and physical examination has been conducted and hirsutism is clinically

evident, finding the source of hirsutism is the next most important step.

Serum androgens: Both the ovaries and the zona reticularis portion of the adrenal cortex produce serum androgens that can lead to hirsutism. The ovaries and adrenals both produce testosterone, and the androgen specific to the adrenal glands is dehydroepiandrosterone sulfate (DHEA-S) (Barbieri 2013).

- *Testosterone* (*T*): Both unbound (free) and total testosterone.
- Total T values above 200 ng/dL or free T values >2.2 pg/mL require further evaluation. Levels above this are suspicious for an androgen-producing ovarian tumor, and a pelvic ultrasound should be performed (Lebovic et al. 2013b).
- Percentage of free T of the total T is 3 % in normal men, 1 % in normal women, and 2 % in hirsute women.
- Some guidelines recommend a 24-h mean value of T levels as androgen secretion is pulsatile and cannot be appropriately evaluated with a single isolated value. Obtaining an isolated total T level can differ by 38 % from a 24-h mean value (Lebovic et al. 2013b; Phipps 2001).
- Measuring total T by equilibrium dialysis or calculating using total T and sex hormone-binding globulin (SHBG) results has been traditionally used, but measuring total testosterone itself readily identifies patients adequately enough, and traditional methods are not necessarily needed to detect androgen-secreting tumors (Miller et al. 2004).
- Most PCOS patients have testosterone concentrations below 200 ng/dL and sometimes in the normal range (19–60 ng/dL). However, a higher androgen level indicates an increased cardiovascular risk even if it does not correlate with the degree of hirsutism (Wild et al. 2010).
- *Dehydroepiandrosterone sulfate (DHEA-S)*: An adrenal androgen that, if found >700 mcg/dL, is concerning for an androgen-producing tumor or carcinoma of the adrenal gland. An adrenal CT should be performed with this lab finding (Lebovic et al. 2013b).
  - These patients typically present with Cushing's syndrome alone (45 %), or a mixed Cushing's syndrome and virilization (25 %), or virilization alone (<10 %) (Barbieri and Ehrmann 2013a).

17-Hydroxyprogesterone: This hormone is of particular interest to women of Ashkenazi Jewish descent as they are at higher risk for having nonclassic 21-hydroxylase deficiency (Speiser 2001).

- 17-OHP levels >800 are abnormal. Intermediate results between 200 and 800 ng/dL during the morning follicular phase of the menstrual cycle need further screening. Levels >1500 ng/dL in response to a cosyntropin (ACTH) stimulation test confirm CAH (Barbieri and Ehrmann 2013a).
- Dexamethasone 0.5 mg PO every 6 h × 2 days can be administered, and DHEA-S and 17-OHP are measured before and after the steroid course.
  - If levels do not decrease or are unchanged, Cushing's syndrome is the likely diagnosis.
  - If the levels decrease, the suspected diagnosis is nonclassical congenital adrenal hyperplasia versus PCOS. Decreased overall cortisol is the normal response to a dexamethasone suppression test in a patient without Cushing's syndrome.
- 17-OHP is drawn during the early follicular phase as it is normally elevated in the luteal phase of the menstrual cycle.
- Progesterone (P4) can be drawn with 17-OHP to ensure the patient is not in the luteal phase of the menstrual cycle, when 17-OHP is normally elevated. It should be <3 ng/mL (Lebovic et al. 2013b).

Estradiol and follicle-stimulating hormone: These hormones are both decreased in hypogonadotropic hypogonadism. In premature ovarian

failure, estradiol is decreased, while FSH is increased (Lebovic et al. 2013b). In the absence of estradiol, sex hormone-binding globulin levels decrease, and free T levels increase.

24-hour urinary cortisol: Women presenting with hirsutism that also have signs and symptoms of Cushing's syndrome such as central obesity, multiple dark and purple striae, hypertension, and the characteristic "buffalo hump" on the back of their neck should have a 24-h urinary cortisol performed (Barbieri and Ehrmann 2013a). Values three times the upper limit of normal (the normal value is 50 mcg/24 h) are considered diagnostic (Lebovic et al. 2013b).

Prolactin: Pituitary tumors such as prolactinomas can lead to ovulatory dysfunction that may result in hirsutism. The upper limit of normal is 30 ng/mL. Elevated TSH from hypothyroidism can also result in hyperprolactinemia, and therefore a thyroid panel should be obtained as well.

Thyroid-stimulating hormone: Increased TRH in hypothyroidism can also stimulate prolactin release and cause ovulatory dysfunction, and thyroid disease without any effect on prolactin levels can lead to ovulatory dysfunction (Lebovic et al. 2013b).

Glucose tolerance testing: Insulin resistance is common in PCOS patients in both obese patients and those with a normal BMI. Glucose tolerance testing should be performed every 1–2 years in patients with PCOS. HgBA1C values of 5.7–6.4 % indicate potential glucose intolerance, and values greater than or equal to 6.5 % confirm diabetes (Lebovic et al. 2013b). Some studies have demonstrated a greater detection of glucose intolerance with a 2-h GTT compared to HgBA1C.

Lipid profile: Although not a direct cause of hirsutism, a lipid profile should be routinely monitored as patients with hyperandrogenism are at risk for hyperlipidemia. Total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride levels should be obtained (Lebovic et al. 2013b).

Endometrial biopsy: Surveillance of the endometrium should also be considered with a patient with PCOS, especially if they are obese. Both obesity and PCOS result in chronic unopposed estrogen stimulation of the endometrium and place the patient at an increased risk for endometrial cancer (Lebovic et al. 2013b).

Pelvic ultrasonography: Although androgen-secreting sex cord stromal tumors are not typically visualized on pelvic ultrasound (Demidov et al. 2008), this imaging modality is still a safe and effective method of evaluating ovarian morphology and should be performed if an ovarian androgen-secreting tumor is suspected or if PCOS is suspected. Women with PCOS will characteristically have 12 or more follicles of 2–9 mm per ovary and/or an ovarian volume of 10 mL or more (Barbieri and Ehrmann 2013a). Findings that are suspicious include large cysts, solid masses, and complex cysts that are found to be persistent after 2–4 weeks after reevaluation (Demidov et al. 2008).

Adrenal imaging: Computed tomography (CT) with contrast of the adrenals should be performed if a woman has a rapid onset or progressive course of virilization or severe hirsutism or if androgens are significantly elevated. This image can also be done with ovarian and adrenal vein sampling for further evaluation in order to discover the etiology of the severely elevated testosterone levels (Barbieri and Ehrmann 2013a).

A summarization of clinical features and laboratory values is given in Table 1. Figure 3 shows the hyperandrogenism evaluation algorithm.

5 Treatment

When it comes to treatment of hirsutism and acne, it is extremely important to take into consideration the patient's perception of how she feels. Hirsutism and acne present on a spectrum of severity, and a woman with scant hirsutism may be significantly more insecure about her physical appearance than a woman with severe hirsutism, for example. Women with hyperandrogenism also have additional comorbidities that need to be addressed and treated such as obesity, diabetes

Table 1 Summarization of the common etiologies, clinical features, and laboratory values pertaining to hirsutism. *TVUS* transvaginal ultrasound

Etiology (common)	Clinical features	Laboratory values
PCOS	Peripubertal onset, oligomenorrhea, obesity, hyperandrogenism, 12 or more follicles on TVUS, ovarian volume of 10 mL or more	Total T levels: increased DHEA-S: increased LH-FSH ratio, typically > 2:1 None of the above results are necessary for the diagnosis
Idiopathic hirsutism	Normal menses, no identifiable cause	Normal androgen levels
Nonclassic 21-hydroxylase deficiency	Similar to PCOS presentation, peripubertal	17-OHP: >800 ng/dL or >1500 after ACTH stimulation test Androstenedione: increased
Classic 21-hydroxylase deficiency	Early onset/diagnosed during infancy, ambiguous genitalia	17-OHP: >800 ng/dL or >1500 after ACTH stimulation test Androstenedione: increased
Androgen-secreting ovarian tumor (Sertoli-Leydig cell, granulosa-theca cell)	Late onset (usually later than third decade). Sudden and rapid hirsutism onset. Virilization	Total T level: >200 ng/dL Ovarian tumor on transvaginal ultrasound
Androgen-secreting adrenal tumor	Commonly mixed Cushing's and virilization syndrome. Some just with virilization	DHEA-S: >700 mcg/dL Adrenal tumor on CT abdomen
Cushing's disease	Central obesity, multiple dark and purple striae, hypertension, "buffalo hump" on the neck	24-h urine cortisol: 3 x's upper limit of normal (at least 150 mcg/24 h) Other screening tools include midnight salivary cortisol and the overnight dexamethasone suppression test
Drugs	Exogenous steroids, danazol, acetazolamide, metoclopramide, methyldopa, methyldopa, progestins, reserpine (Lebovic et al. 2013c)	Abnormal toxicology screen

mellitus, oligoovulation/infertility, and endometrial hyperplasia/cancer (Barbieri 2013). Therefore, the main goals in treatment of women with hirsutism should of course be improving her hirsutism and acne and also prevention of endometrial hyperplasia/cancer, restoration of normal menstruation (if not desiring fertility), and enhancing fertility (if desiring children) (Lebovic et al. 2013c).

The patient should be periodically assessed on her own perception of treatment and asked if she has noted a decrease in the need to utilize cosmetic methods such as shaving, plucking, and waxing. Additionally, the routine monitoring of serum androgens to assess a response to drug therapy is not necessary (Lebovic et al. 2013c). The average half-life of a hair follicle is approximately 6 months. Therefore, reduction in hair growth may not occur for up to 6 months. After this assessment point, drug dosages may be altered, another drug added to the current regimen, or an alternative drug may be utilized. All women wanting to conceive should discontinue the use of antiandrogens, as this may alter male sexual development (Lebovic et al. 2013c).

5.1 Weight Reduction

Restoration of normal cyclic menses and therefore fertility can be achieved in up to 75 % of women who only lose as little as 5–7 % of their overall body weight. Weight reduction will also improve insulin sensitivity and subsequently reduce hyperandrogenism. To help put things into perspective, a 200-lb patient seeking treatment for hirsutism and fertility will only need to lose 10–15 lb to improve her symptoms. This can easily be achieved over the course of a few short months with a low-calorie diet (1,000–1,500 kcal/day) and exercise and can also be supplemented with metformin to aid in insulin sensitivity (Lebovic et al. 2013c).

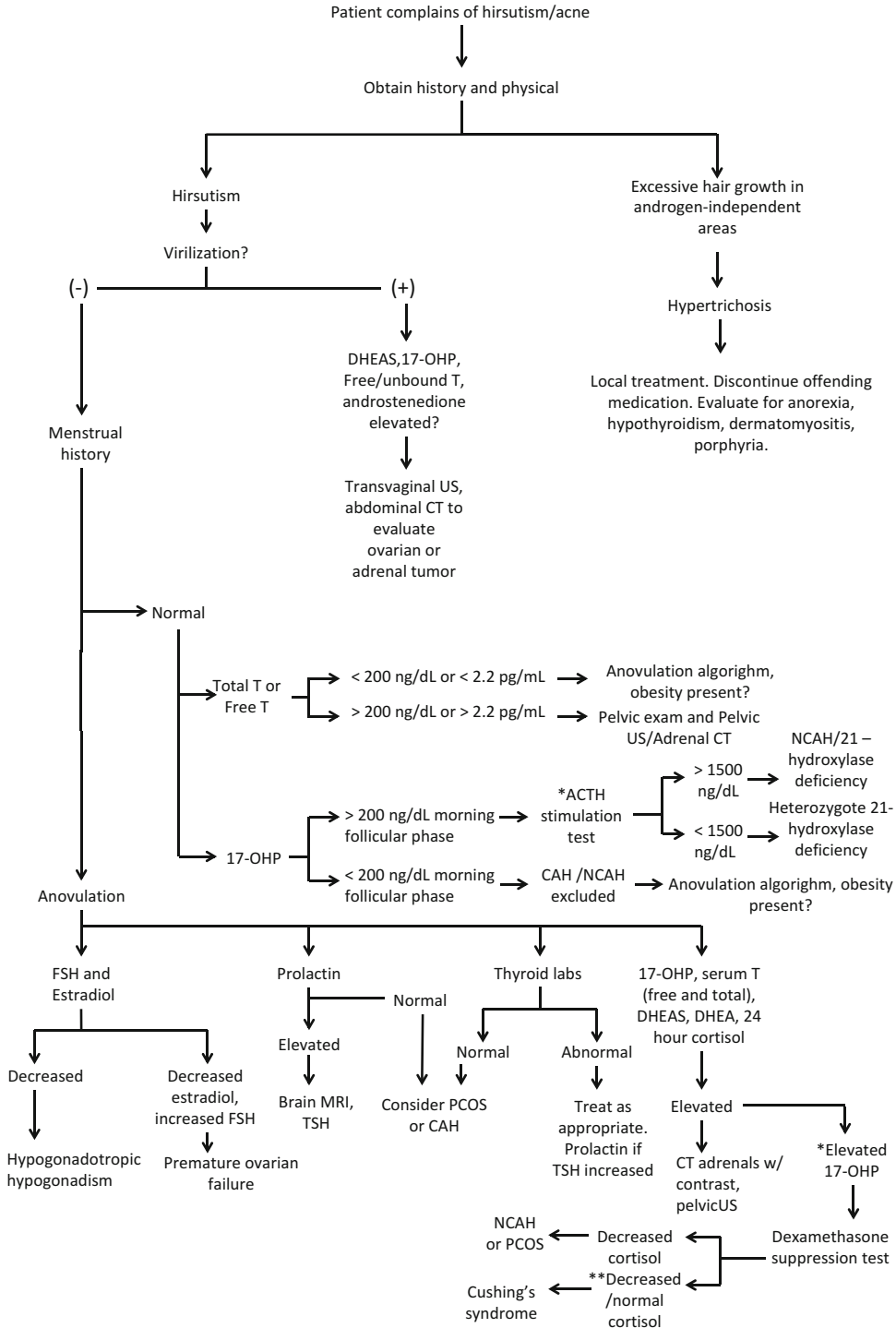

Fig. 3 Hyperandrogenism evaluation algorithm. *Elevated 17-OHP levels can be evaluated by a dexamethasone suppression test and/or an ACTH (cosyntropin) stimulation test. **A lower dexamethasone dose should normally elicit a decreased overall cortisol. In Cushing's syndrome, a low-dose dexamethasone results in no change in cortisol levels, and a higher dose of dexamethasone results in suppression of cortisol (Schorge and Williams 2008a)

5.2 Hair Removal Treatments

In order to receive optimum suppression of hirsutism symptoms, nonpharmacological treatment methods such as hair removal should be supplemented with antiandrogens in order to prevent regrowth (to be discussed later) (Barbieri 2013). The most cost-effective approaches include shaving, plucking, waxing, and bleaching. However, there are permanent hair reduction methods that can be utilized including electrolysis and laser-assisted hair removal (photoepilation) (Barbieri 2013).

Electrolysis is a relatively expensive method that is also somewhat painful and time-consuming. It involves placement of a needle within hair follicles and initiates an electric current that destroys the hair follicle. The most effective method involves a blend of galvanic electrolysis and thermolysis (Lebovic et al. 2013c).

Laser-assisted hair removal (photoepilation) usually involves four to six treatments utilizing thermal destruction to follicular melanin and has most optimum results if the patient waxes prior to the procedure. This method works best in patients who have light skin with dark hair and may cause pigment changes: hypopigmentation or hyperpigmentation. This method should also be avoided in patients who have a tendency to form keloids or hypertrophic scars (Lebovic et al. 2013c).

5.3 Oral Contraceptives (OCPs)

OCPs are the first-line drug treatment of choice for treatment against acne, but severe hirsutism will usually require the addition of an antiandrogen to the treatment regimen (Lebovic et al. 2013c). Between 60 % and 100 % of hyperandrogenic women treated with OCPs experienced a significant reduction in hair growth (Barbieri 2013). Although most data is derived from studies utilizing OCPs, transdermal and vaginal estrogen-progestin formulations are considered to be effective as well (Barbieri 2013).

OCPs treat hyperandrogenism by increasing hepatic production of SHBG levels (increased estrogen→increased SHBG→decreased levels of unbound free T from both the ovaries and adrenal glands), suppressing LH via negative feedback (usually suppressed to normal levels), and inhibiting 5-alpha-reductase and androgen receptor binding. For women with PCOS, OCPs have the additional benefit of decreasing the risk for endometrial hyperplasia.

Typically, OCPs containing 30–35 micrograms of ethinyl estradiol are used, and switching to the lower dose of 20 micrograms in women over 40 years of age reduces the risk of endometrial malignancies and deep venous thrombosis risk (Barbieri 2013). Progestins such as levonorgestrel should be avoided when prescribing OCPs as this progestin has androgenic properties. However, progestins should be considered every 2–3 months to prevent endometrial hyperplasia, a known risk factor of patients with chronic anovulation (Lebovic et al. 2013c). Carr et al. conducted a study to determine whether or not a gonadotropin-releasing hormone agonist plus add-back therapy would be better treatment than OCPs alone and concluded that this treatment was no better than OCPs alone (Carr et al. 1995).

5.4 Antiandrogens

Antiandrogens are often given in addition to OCPs if the patient has severe hirsutism. It is imperative to keep women on OCPs or some other form of contraception while taking antiandrogens as incomplete virilization of a male fetus may occur (Lebovic et al. 2013c). These women must be counseled on the importance of contraception compliance while taking antiandrogens as most antiandrogens are category × in pregnancy.

- **Spironolactone (Aldactone)** of 50–200 mg/day in addition to taking OCPs is a common regimen used for treatment of severe hirsutism. Spironolactone works by inhibition of aldosterone, inhibition of steroidogenic enzymes, and binding to androgen receptors located on the hair follicle. This medicine is relatively inexpensive, comes in a generic form, and is

commonly prescribed. Additionally, irregular uterine bleeding, hyperkalemia, and gastrointestinal discomfort are common side effect of spironolactone (Lebovic et al. 2013c).

- **Finasteride** is an excellent and safe antiandrogen that is a type 2 5-alpha-reductase inhibitor, although its use for hirsutism is considered "off-label." It prevents the conversion of T to DHT. Administering a low dose of 2.5–5 mg/day every 3 days has proven effective. Failure to take contraception while on finasteride can increase the risk of hypospadias and other genital abnormalities in male fetuses (Lebovic et al. 2013c).
- **Cyproterone acetate (Androcur)** is a derivative of 17-hydroxyprogesterone that decreases 5-alpha-reductase activity and acts as an androgen receptor antagonist. It also competes with DHT binding sites on androgen receptors and reduces serum LH levels/ovarian androgen concentrations. Although this medication is used extensively in Europe and Israel, its use is not FDA approved in the United States as studies have reported liver tumors in beagles that have taken Androcur (Lebovic et al. 2013c).
- **Flutamide** is similar to Androcur in that it is an androgen receptor antagonist. Flutamide is nonsteroidal and is used primarily in the treatment of prostate cancer. However, it has been used as an off-label medication to treat hirsutism and is not FDA recommended as its use is associated with hepatotoxicity. A recommended treatment regimen is 250–750 mg/day (Barbieri 2013).
- **Eflornithine**: Ornithine decarboxylase (ODC) is an enzyme required to synthesize follicle polyamines necessary for hair growth. Eflornithine irreversibly inhibits ODC, and reduction in hirsutism is seen over 4–8 weeks. If the medicine is discontinued, hirsutism will return. This medication is also available as an eflornithine hydrochloride 13.9 % cream for the use of unwanted facial hair (Barbieri 2013). The main disclaimers pertaining to this medication are that it may cause skin irritation in a small percentage of patients and that it is also a category C drug (Lebovic et al. 2013c).

5.5 Insulin-Sensitizing Agents

Metformin has been used to restore ovulatory cycles and lower insulin resistance in patients with PCOS, but it is not recommended for routine treatment of hirsutism and acne (Barbieri 2013). Metformin is a biguanide oral hypoglycemic agent that inhibits hepatic glucose production and increases peripheral insulin sensitivity. As circulating insulin levels are decreased from its use, LH levels as well as free testosterone and plasminogen activator inhibitor-1 levels are also decreased (Lebovic et al. 2013c). Although there is evidence revealing possible efficacy in hirsutism treatment and one would presume from its mechanism of action that it would reduce hyperandrogenism, multiple studies reveal no statistically significant reduction in Ferriman-Gallwey scores when using metformin compared to placebo use (Cosma et al. 2008).

5.6 Other Treatment Modalities

Although it is not routinely recommended per the 2008 Endocrine Society guidelines, it is relatively expensive, and there are other more effective hirsutism treatment modalities available, the use of a GnRH agonist with supplementation of add-back therapy can be used in women who have hypertension as a comorbidity. Add-back therapy typically entails a combination OCP or a low-dose progesterone. Progesterone therapy is important to reduce bone mineralization loss, and OCP add-back therapy reduces the adverse effects of estrogen deficiency without altering the GnRH agonist treatment properties (Barbieri 2013).

Additionally, the routine use of glucocorticoids is not recommended for treatment of hirsutism per the 2008 Endocrine Society guidelines. They have been used in the past with women who have classic 21-hydroxylase (CYP21A2) deficiency and women with the nonclassic CYP21A2 deficiency but only with minimal effectiveness (Barbieri 2013). One exception would be a patient with nonclassical congenital adrenal hyperplasia who does not respond to or does not respond well

Table 2 Treatment of acne. [a]Oral antibiotics include tetracycline, doxycycline, minocycline, erythromycin, trimethoprim-sulfamethoxazole, clindamycin, and azithromycin (Grabber 2015)

Comedonal (noninflammatory)	Mild papulopustular and mixed acne	Moderate papulopustular and mixed acne	Moderate nodular acne	Severe nodular/ conglobate acne
Topical retinoid (azelaic acid or salicylic acid)	Topical retinoid + topical antimicrobial (i.e., benzoyl peroxide) +/− topical antibiotic (erythromycin and clindamycin, sulfacetamide, or dapsone)	Topical retinoid + oral antibiotic[a] + topical benzoyl peroxide	Topical retinoid + oral antibiotic + topical benzoyl peroxide	Oral isotretinoin

to the use of OCPs and antiandrogen therapies. In theory, glucocorticoid administration will suppress hypothalamic corticotrophin-releasing hormone (CRH), which in turn will decrease ACTH and subsequently adrenal androgen production. Although these medications do effectively suppress serum DHEA and DHEA-S, they are less effective than OCPs at decreasing hirsutism scores (Barbieri 2013).

5.7 Postmenopausal Women

Prior to initiating treatment, an androgen-secreting tumor must be ruled out in postmenopausal women with the sudden onset of hirsutism. Treatment options typically entail an antiandrogen in addition to a low-dose estrogen. If a postmenopausal woman has hyperthecosis and severe hirsutism, a bilateral oophorectomy should be considered (Barbieri 2013).

5.8 Treatment of Acne

Although treatment of the underlying hyperandrogenism will eventually treat the patient's acne, there are various treatment regimens for acne treatment including oral treatments, topical treatments, and a combination of the two (Table 2). Typically, acne is treated based on the severity of the presentation. This spectrum includes comedonal (or noninflammatory) acne, mild papulopustular and mixed (comedonal and papulopustular) acne, moderate papulopustular and mixed acne, moderate nodular acne, and severe nodular/conglobate acne (Grabber 2015). It is mandatory that patients take birth control when taking any oral acne medication, and most topical acne medications are category C and should be used sparingly. Of the oral antibiotics, trimethoprim-sulfamethoxazole, tetracycline, and minocycline are contraindications to pregnancy and should only be given when the patient is using contraception. Some dermatologists will not prescribe an oral isotretinoin unless the patient is on two forms of contraception. Following is a brief and general approach to the treatment of acne (Grabber 2015).

6 Conclusion

In conclusion, hyperandrogenism (with PCOS being the most common culprit) is an extremely common pathology among women. Aside from hirsutism causing psychological distress and insecurities of a woman's physical appearance, hirsutism is commonly affiliated with particular comorbidities including endometrial hyperplasia, hyperlipidemia, infertility, diabetes mellitus, CAH, and adnexal/adrenal masses. A full workup is warranted in order to initiate appropriate treatment to alleviate the etiology of the hyperandrogenism and subsequently alleviate hirsutism and acne. Not only will a full workup identify the etiology of the hyperandrogenism, but comorbidities such as hyperlipidemia and diabetes mellitus requiring long-term monitoring and treatment can be identified as well.

7 Cross-References

- Counseling and Management of Obesity in Association with Gynecologic Diseases
- Gynecologic History and Examination of the Patient
- Impact of Obesity on Gynecological Diseases

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Hyperprolactinemia, Galactorrhea, and Pituitary Adenomas

Kate C. Arnold and Caroline J. Flint

Contents

Abstract

Pituitary adenomas, hyperprolactinemia, and galactorrhea are disorders which can occur concomitantly or independently. In the following chapter, we will discuss the differential, signs and symptoms, and diagnosis of these diseases. Pituitary adenomas are classified by their size with less than 1 cm being a microadenoma and equal to or greater than 1 cm being a macroadenoma. They can be additionally delineated as functioning versus nonfunctioning based on their hormone production status. Prolactin is synthesized in the pituitary and is primarily controlled by suppression with dopamine. Elevations may be due to many causes including prolactinomas, stalk compression, medications, or hypothyroidism. Galactorrhea may be due to prolactin elevations or may be unrelated. The chapter includes a discussion of both medical and surgical therapy options as well as a discussion regarding management during pregnancy. Generally, medical therapy involves treatment with dopamine agonists to suppress prolactin, although hormonal therapy with combined oral contraceptives or cyclic progestin is a reasonable alternative. In patients that are resistant to first time medications at their maximum dose, surgical management should be considered.

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1 Introduction to the Pituitary and Pituitary Adenomas

In patients who present who problems relating to nipple discharge and/or changes in their menstrual cycle, a diagnosis of hyperprolactinemia should be considered. Understanding hyperprolactinemia and its clinical correlates can aid significantly in correctly diagnosing this disorder. Doing so can be difficult because it requires an understanding of the anatomy, neurology, physiology, and endocrinology of the pituitary and its receptor organs.

Given that it may have been years since sitting in a classroom, we will review the basics at this time. An adenoma is a benign growth formed from glandular structures in epithelial tissue. Adenomas are classified by size; a macroadenoma is 1 cm or greater in diameter and a microadenoma is less than 1 cm. They are further organized by either being functioning, meaning that they secrete hormones, or nonfunctioning (Samarasinghe et al. 2014).

The differential diagnosis for a pituitary mass includes a multitude of disorders including pituitary hyperplasia, lymphocytic hypophysitis, granulomatous hypophysitis, sarcoidosis, pituitary abscess, craniopharyngioma, Rathke's cleft cyst, pars intermedia cyst, colloid cyst, arachnoid cyst, empty sella, germ cell tumors, hamartoma, astrocytoma, aneurysm, histiocytosis, chordoma, and metastatic carcinoma (Samarasinghe et al. 2014). Despite this extensive differential diagnosis, the most common cause by far is the adenoma. Also common is pituitary hyperplasia, which is generally due to the physiologic changes associated with pregnancy, leading to lactotroph hyperplasia (Samarasinghe et al. 2014).

In the case of pituitary apoplexy, acute symptoms can develop including changes in vision, nausea, or sudden onset of severe headache. Pituitary apoplexy occurs when an existing adenoma has outgrown its own blood supply which results in pituitary hemorrhage. Alternatively, this can occur when the growing adenoma compresses the stalk, which subsequently slows the flow of venous blood return. Treatment of this acute phenomenon typically requires immediate corticosteroids administration as death can occur due to adrenal insufficiency. The steroids have an added benefit of decreasing associated inflammation and help prevent the occurrence of mass effect (Samarasinghe et al. 2014).

Nonfunctioning adenomas may be asymptomatic or may cause significant dysfunction, as stated, due to mass effect or via hormone alterations. If a macroadenoma is present, the resulting side effects will be directly related to the speed by which the mass grew, the size, and the location of the adenoma (Samarasinghe et al. 2014). When a pituitary adenoma is incidentally found, a workup is indicated. Necessary testing includes prolactin, IGF-1 to screen for acromegaly, cortisol levels to screen for Cushing's disease, and visual field testing. Approximately 10 % of microadenomas and 24 % of macroadenomas will progress in size. Conservative management can be undertaken if no changes in hormone levels are noted and there are no mass symptoms present. This includes surveillance with repeat imaging to monitor for change in size (Samarasinghe et al. 2014).

2 Prolactin

Prolactin is synthesized by the pituitary lactotrophs (Melmed et al. 2011) in the anterior pituitary in both physiologic situations, as well as pathologic states (Romijin 2014).

Prolactin synthesis is suppressed by dopamine, which acts on the D2 receptors in the anterior pituitary (Melmed et al. 2011). Dopamine is synthesized in the hypothalamus and delivered to the anterior pituitary via the pituitary stalk (Romijin 2014). Prolactin production is increased by estrogen, thyrotropin-releasing hormone (TRH), epidermal growth factor, and dopamine receptor antagonists (Melmed et al. 2011). The production of prolactin is uniquely regulated in comparison to other hormones of the anterior pituitary in that it is

modulated by suppression, rather than stimulation (Samarasinghe et al. 2014). Additionally dopamine not only inhibits the release of prolactin, but it also inhibits prolactin gene expression and lactotroph proliferation (Samarasinghe et al. 2014).

Prolactin induces and maintains female breast lactation (Melmed et al. 2011). During pregnancy, prolactin increases and stimulates the alveoli in the mammary glands to generate milk (Romijin 2014). Hyperprolactinemia outside of pregnancy can be caused by prolactinomas, adenomas, and changes in dopamine regulation or can be idiopathic (Melmed et al. 2011). Prolactinomas account for up to 40 % of pituitary tumors (Melmed et al. 2011).

Pituitary tumors and parasellar masses can indirectly result in increased prolactin levels by means of stalk compression which prevents the delivery of dopamine. As mentioned, dopamine inhibits the secretion of prolactin, so if this is blocked then a rise in prolactin will be observed (Melmed et al. 2011).

A prolactin cutoff of 94 μg/l has been proposed to distinguish between a prolactinoma and a nonfunctioning adenoma. This distinction is important as it dictates treatment modalities. In patients with nonfunctioning adenomas that are indirectly increasing prolactin levels by means of compression, dopamine agonist can be used to treat symptoms of hyperprolactinemia; however, this will not treat the actual mass. In patients with prolactinomas, dopamine agonists will both treat the tumor and reduce its size (Melmed et al. 2011).

3 Galactorrhea

Galactorrhea is defined as nonphysiologic mammary secretion of milky fluid, meaning that it occurs outside of the peripartum period. Generally, this is persistent, and colors of expressed fluid range from clear white to even yellow or green. Secretions associated with hormonal causes are from multiple ducts, as opposed to pathologic causes, which are from single ducts. Any bloody secretions should raise the suspicion for cancer (Fritz and Speroff 2011). Elevated prolactin levels inhibit the release of gonadotropin-releasing hormone (GnRH) and therefore affect the secretion of luteinizing hormone (LH). Effects in luteinizing hormone (LH) production can lead to changes in menstrual cycle regularity and fertility (Romijin 2014).

Idiopathic galactorrhea should be suspected in women with galactorrhea in the presence of normal menstrual cycles that is not associated with pregnancy. This usually indicates a normal prolactin level (Romijin 2014).

Approximately only one-third of women with hyperprolactinemia will also have galactorrhea. This is due to the fact that estrogen plays an important role in galactorrhea and hyperprolactinemia generally causes a decrease in estrogen (Fritz and Speroff 2011). A broad differential is important in considering the cause of galactorrhea. Although prolactin elevation is a common cause, other causes include drugs, hypothyroidism, excessive estrogen, prolonged suckling or nipple piercing, stress, and renal disease (Fritz and Speroff 2011).

If galactorrhea is due to hyperprolactinemia, it generally resolves with treatment of the hyperprolactinemia (Melmed et al. 2011).

4 Signs and Symptoms of Prolactinomas

Masses arising in the pituitary can become symptomatic by two different mechanisms: mass effect and endocrine changes. The pituitary is located within the sella turcica behind and above the sphenoid sinus. It weighs less than one gram and is composed of an anterior and posterior compartment. When a pituitary tumor becomes too large for the sella turcica, it begins to compress on the optic chiasm and can subsequently cause vision changes (Samarasinghe et al. 2014).

Generally only macroadenomas cause mass symptoms. Most often, the vision changes are gradual, so a patient may not be aware of their deficiency until they are given formal visual field testing. The most common deficit in vision noted is termed bitemporal hemianopsia, which is defined as the loss of vision in the temporal fields

due to direct compression of the optic chiasm (Samarasinghe et al. 2014). If the mass extends laterally, it can lead to cranial nerve palsies, primarily of cranial nerve 3, 4, 5, and 6. Symptoms with cranial nerve 3 are the most commonly experienced and result in a patient having difficulty moving their eye muscles normally. Changes in cranial nerve 5 are generally due to apoplexy (Samarasinghe et al. 2014).

Headaches are incredibly common in patients with macroadenomas and even microadenomas. The cause of this is not known. Generally, symptoms improve after surgical or medical treatment (Samarasinghe et al. 2014).

Clinical effects of hyperprolactinemia may include hypogonadism, infertility, and galactorrhea, or it may be asymptomatic (Melmed et al. 2011). Decreased levels of gonadotropin-releasing hormone (GnRH) cause decreased follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which leads to these downstream effects. The decrease in GnRH can also lead to bone loss due to sex steroid attenuation. In some cases, spine bone density can decrease up to 25 % and may not be restored despite adequate treatment (Melmed et al. 2011).

Women with hyperprolactinemia specifically may experience menstrual disorders including primary amenorrhea (menstruation never starting) or secondary amenorrhea (cessation of menstrual cycles). Generally, with high levels of prolactin, the patient is more likely to be amenorrheic, whereas with levels less than 100, the patient will likely experience oligomenorrhea or infrequent menses (Fritz and Speroff 2011). Hyperprolactinemia may also lead to delayed menarche and infertility (Romijin 2014). Because of decreased ovulation, hirsutism is a common complaint as well (Fritz and Speroff 2011).

Women may complain of decreased libido and pain with intercourse (2, 3). In adolescence, girls can present with disturbances in menses or galactorrhea. In boys, it may present with delayed puberty and hypogonadism. Treatment does not differ in these two groups (Melmed et al. 2011).

5 Diagnosis of Hyperprolactinemia

Diagnosing hyperprolactinemia is simple and only requires a single lab test revealing an elevated serum prolactin. The World Health Organization (WHO) defines hyperprolactinemia as a prolactin level above 25 μg/l. If serum prolactin is found to be elevated, a repeat or confirmatory testing is not recommended to establish the diagnosis of hyperprolactinemia. The test may be performed at any time of the day. If the prolactin level is found to be within normal limits, but one has high clinical suspicion, then a repeat test can be performed as variations can be seen due to pulsatility of hormone production (Melmed et al. 2011). The prevalence of clinically relevant hyperprolactinemia ranges from 6 to 50/100,000 people (Melmed et al. 2011).

Macroprolactin is a large, polymeric form of prolactin that may be associated with autoantibodies. It is recommended that patients be screened for the presence of macroprolactin if hyperprolactinemia is found in an asymptomatic patient. These large forms of prolactin are often less biologically active (Melmed et al. 2011).

A thorough physical examination is important in patients who are found to have hyperprolactinemia, as it may be a symptom of another disorder. For example, over half of patients with a growth hormone-secreting tumor, which leads to acromegaly, will also have elevated prolactin levels (Melmed et al. 2011). Acromegaly causes clinical features related to the overgrowth of many tissues. Physical exam findings consist of enlargement of the nose and frontal bones, enlarged tongue, coarse facial features, and swollen hands and feet (Fritz and Speroff 2011).

If a patient is found to have a large pituitary tumor but a relatively low prolactin level, serial dilution of the serum samples should be performed to test for the hook effect. The hook effect occurs when the concentration of the sample is so high that it saturates the antibodies in the assay, which results in the signaling antibody in the sample resulting as falsely low. Diluting the sample will overcome this effect, as will a

washout to eliminate the unbound prolactin. If the sample is diluted, it will distinguish between a large prolactinoma, which will have a high prolactin, and a large nonfunctioning adenoma (Melmed et al. 2011).

In prolactinomas, the prolactin level is generally correlated with the size of the tumor, and, as mentioned, most patients with a level above 250 μg/l will have a prolactinoma (Melmed et al. 2011).

6 Imaging

The treatment of an adenoma may depend on the size and location of the lesion and its resulting symptoms caused by mass effect. Given this, obtaining detailed imaging of the lesion is very important. An optimal report should describe the displacement of adjacent structures the size shape, and location of the mass and the density of the mass. MRI is the ideal modality and should be focused on the sellar region. Without this specification, the cuts obtained generally do not provide the necessary detail. If done well, the pituitary stalk, pituitary, optic tracts, and sinuses can all be visualized as distinct entities (Samarasinghe et al. 2014).

7 Diagnosing the Cause of Hyperprolactinemia

There are various physiologic, pathologic, and pharmacologic causes of hyperprolactinemia. Physiologic causes include nipple stimulation, pregnancy, and stress. Pathologic causes include diseases of the pituitary and hypothalamus as well as decreased clearance of prolactin. Pharmacologic causes generally include drugs that serve as dopamine antagonists, which indirectly elevated levels of prolactin as discussed earlier (Romijin 2014).

A macroprolactinoma is suspected when a prolactin level is found to be greater than 500 μg/l. Levels around 200 μg/l generally indicate a prolactinoma; however, this can also be seen with the use of antipsychotic drugs like risperidone and metoclopramide (Melmed et al. 2011). Other studies suggest that a cutoff of 94–100 μg/l detects the presence of a prolactinoma as opposed to a nonfunctioning mass. Below this cutoff, the elevation in prolactin is likely due to stalk compression.

In patients with symptomatic nonphysiological hyperprolactinemia who do not have a tumor, medication use, renal failure, and hypothyroidism should all be considered in the differential diagnosis (Samarasinghe et al. 2014).

Renal insufficiency can cause moderate elevations in prolactin due to slowed clearance of serum prolactin. Production can also be increased in these patients. Dialysis does not decrease serum levels; however, levels are noted to normalize following renal transplants. In patients with hyperprolactinemia due to renal disease who have hypogonadal symptoms, bromocriptine therapy can lead to resumption of menses (Melmed et al. 2011).

Hypothyroidism that is chronic or not adequately treated can cause pituitary hyperplasia, which may lead to hyperprolactinemia. This can be reversed when the hypothyroidism is adequately treated with levothyroxine. Thus, close attention must be paid to the thyroid exam as part of a workup for hyperprolactinemia (Melmed et al. 2011).

In patients with idiopathic hyperprolactinemia, spontaneous return to normal levels of prolactin occurs in one-third of patients (Melmed et al. 2011).

Typical prolactin levels associated with medication use are approximately 25 micrograms to 100 micrograms; however, metoclopramide, risperidone, and phenothiazines can lead to more elevated levels, as these antipsychotic drugs serve as dopamine antagonists (Melmed et al. 2011). The calcium channel blocker verapamil can also lead to hyperprolactinemia in 8.5 % of patients. Other drugs that may cause mild elevations in prolactin include opiates or estrogen-containing drugs such as oral contraceptives. It is recommended that asymptomatic hyperprolactinemia due to medications not be treated (Melmed et al. 2011).

8 Management of Hyperprolactinemia Due to Medications

If the physician suspects that a patient's hyperprolactinemia is due to a medication, there are two options. One is to stop the medication for 3 days and redraw the serum prolactin. If normalized, no further work-up is needed. If it is not possible to stop the medication, or the timing of the medication does not correlate with the hyperprolactinemia, an MRI of the head should be obtained to rule out a pituitary or hypothalamic mass (Melmed et al. 2011). In patients without a tumor, medications are the most common cause of hyperprolactinemia (Melmed et al. 2011).

In the case of antipsychotics causing hyperprolactinemia, the patient and physician must consider the risks and benefits of stopping the drug versus continuing it. This discussion must include available alternatives such as atypical antipsychotics (Melmed et al. 2011). Treatment is not recommended for patients with asymptomatic medication-induced hyperprolactinemia (Melmed et al. 2011), although estrogen or testosterone may be given in patients with hypogonadal symptoms (Melmed et al. 2011).

As stated above, the most common medications are typical antipsychotics. Hyperprolactinemia is found in 40–90 % of patients taking typical antipsychotics and in 50–100 % of patients taking risperidone (Melmed et al. 2011). Patients may remain asymptomatic. Other times, women develop galactorrhea and amenorrhea, and men develop low libido and erectile dysfunction (Melmed et al. 2011).

9 Medical Management

Medical management is first attempted with dopamine agonists to inhibit hyperprolactinemia. Adequate treatment with a dopamine agonist can normalize prolactin levels, decrease galactorrhea, restore menses, and decrease tumor size. Options include bromocriptine, cabergoline, and quinagolide (Samarasinghe et al. 2014).

First line treatment is cabergoline because it has a high affinity for the D2 lactotroph receptor and is associated with fewer side effects than bromocriptine (Samarasinghe et al. 2014). Decreases in tumor size and decrease in visual field deficits can be seen after several weeks of therapy (Samarasinghe et al. 2014) with normalization in prolactin in 85 % of patients (Romijin 2014). Bromocriptine must be taken two to three times per day in doses of 2.5–15 mg, while cabergoline, which has a half-life of 65 hours, can be dosed once to twice weekly (Romijin 2014).

In counseling patients regarding possible side effects, it is important to include gastrointestinal symptoms and orthostatic hypotension, both of which can be reduced by using dose titration (Samarasinghe et al. 2014).

When initiating patients on dopamine agonists for prolactinomas, prolactin should be measured 1 month after starting treatment (Melmed et al. 2011). Visual field testing should also be performed as well as assessment of comorbidities such as galactorrhea and bone loss (Melmed et al. 2011). Medication should be tapered at 2 years if prolactin is normal and no visible tumor is noted on MRI (Melmed et al. 2011).

Alternative managements from the gynecologic perspective include hormonal therapy either in the form of cyclic progestin or combined oral contraceptives. These treatments can decrease the effects of unopposed estrogen. Previous concerns that this may exacerbate hyperprolactinemia have not come to fruition in clinical studies. Treatment with progesterone or combined hormonal therapy protects the patient from the dangers of unopposed estrogen such as endometrial hyperplasia, atypia, and endometrial cancer. Unlike the dopamine agonists, these treatments can be used in patients with medication-induced hyperprolactinemia (Fritz and Speroff 2011).

Prior to consideration of surgery, doses of the dopamine agonist should be titrated to the maximum tolerable dose. There are reports of valvular abnormalities in patients on dopamine agonists at

high doses for prolonged periods of time; hence, echocardiograms in these patients may be reasonable. If bromocriptine has failed, cabergoline should be attempted prior to referral as well (Melmed et al. 2011).

10 Surgical Management

Surgical management is indicated if there is mass effect with visual compromise, the mass is resistant to medical therapy, apoplexy has occurred, or a histological diagnosis is needed. Remission rates after surgery are reportedly 90 % in active pituitary adenomas (Samarasinghe et al. 2014).

The approach for surgery is generally transsphenoidal. This is favored as it is minimally invasive with a low mortality of 0.2–1 %. If the mass is too large/invasive for this approach, a transcranial approach may be necessary (Samarasinghe et al. 2014).

Complications of the surgery include anterior pituitary insufficiency, diabetes insipidus, sinus disease, CSF leak, intracranial hemorrhage, septal perforation, and epistaxis (Samarasinghe et al. 2014).

If surgical treatment fails and the tumor is resistant or malignant, radiotherapy is a reasonable treatment. Malignant is defined as metastatic spread within or outside the central nervous system. These are very rare with only 50 ever having been described (Melmed et al. 2011).

11 Pregnancy

Patients with prolactinomas should stop dopamine agonist prior to pregnancy or upon a positive pregnancy test; however, in patients with macroadenomas, it may be reasonable to continue dopamine agonist treatment. Bromocriptine does cross the placenta; however, the incidence of congenital malformations and abortions are not increased. There is less data regarding cabergoline during pregnancy; but, it does not appear to be harmful (Melmed et al. 2011). Quinagolide, which is not used in the United States, is known to have a high incidence of adverse outcomes during pregnancy and should not be used (Romijin 2014).

Serial measurements of prolactin during pregnancy should not be performed, as these can be difficult to interpret. Imaging should not be performed on patients with microadenomas unless there is suspicion for growth based on a change in visual field testing. If patients do experience systematic growth of a prolactinoma, bromocriptine should be initiated during pregnancy. If visual field is changed or headaches occur, MRI without gadolinium is reasonable (Melmed et al. 2011).

If a patient with hyperprolactinemia is unable to achieve pregnancy, treatment with dopamine agonists can restore fertility in 90 % of patients with cabergoline being the most effective (Romijin 2014). If a dopamine agonist has been used to induce pregnancy, the decision of when to stop the medication is more complex. Generally, patients with macroadenomas are advised to continue their agonist and patients with microadenomas are advised to stop their medication once a pregnancy is achieved. Preference is for bromocriptine as noted above as there is more experience with it in pregnancy. If medications are stopped, monthly evaluations must be done regarding visual field testing or must be counseled regarding seeking care for headaches and vision changes (Romijin 2014).

12 Conclusion

Pituitary adenomas, hyperprolactinemia, and galactorrhea may occur as part of a unified disorder or may be due to a wide differential. In diagnosing the cause for symptoms associated with adenomas and hyperprolactinemia, a good history and physical is always the first step. This may reveal the cause for the symptoms and dictate management decisions. A thorough understanding of how each cause can present with slightly altered symptomatology is also key in managing these patients.

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Basic Management of Infertility

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Contents

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Abstract

In this chapter, the basic management of infertility will be reviewed. An overview of pertinent definitions, evaluation and diagnosis of infertility, and relevant components of history and the physical exam will be discussed. Most importantly, the causes of infertility will be reviewed along with treatments for the specific causes of infertility.

Keywords

Primary infertility • Secondary infertility • Fecundity • Hysterosalpingogram • Chromotubation • Sonohystogram • Assisted reproductive technology • In vitro fertilization

1 Introduction

Infertility is the inability to procreate and a source of anxiety for couples affected. Infertility is a disease that must be investigated in a comprehensive manner. Determining the underlying etiology of infertility specific to the couple, allows for individualized treatments that will increase the chances of conception.

2 Epidemiology

In the United States, approximately 12 % of women have had an appointment for an infertility related concern (Christianson and Wallach 2011). There has been a steady increase in the number of women seeking medical care for infertility over the last several decades. The reasons for the increase remain unclear, but there are many proposed theories. There has been an increase in sexually transmitted infections over time which plays a role in the increasing infertility rates due to tubal occlusion caused by these infections. Over the last several decades, there is increased public knowledge of the medical treatments available for infertility which in turn has increased the rates of those seeking medical attention. Lastly, it is well known that age effects fertility, and with more women delaying child bearing until a later age, this may be a contributing factor to more women seeking medical assistance for infertility (Lobo 2007).

3 Age and Infertility

Women are born with a complete and final set of eggs. By puberty, only about 500,000 eggs remain and the supply continues to decrease by atresia throughout the women's life. As there is a limited supply of eggs, along with other hormonal factors, fertility decreases gradually with increasing age. At age 32, there is a significant decrease in the rate of conception and an even greater decrease at the age of 37. Along with decreasing fertility, there is an increase in miscarriage and aneuploidy with increasing age (Committee Opinion No. 589 2014a).

4 Fecundity

Fecundity refers to the probability of conception in one menstrual cycle. The probability of conception in one menstrual cycle is about 20 %. This percentage increases over time and is cumulative in nature. The vast majority, or about 70 % of women, will have conceived by 6 months and 93 % will have conceived by 2 years. For any couple trying to conceive, it is important to discuss the probability of conception over time and present realistic expectations.

Time in months	Percent pregnant
1	20
3	57
6	72
12	85
24	93

(Guttmacher 1956)

5 Definition of Infertility

Infertility, as defined by the American Society for Reproductive Medicine, is a disease that results in failure to achieve a successful pregnancy by

12 months of timed unprotected intercourse or therapeutic donor insemination (Committee Opinion: Definitions of Infertility and Recurrent Pregnancy Loss 2013). Primary infertility refers to infertility in a woman that has never been pregnant while secondary infertility refers to infertility in a woman that has previously been pregnant.

6 Causes of Infertility

There are several recognized causes of infertility. Understanding and identifying the cause helps the practitioner manage and treat the patient or couple. Several causes are discussed below. It is important to remember when reviewing common causes of infertility that there may be more than one cause and in up to 30 % of couples, a cause cannot be identified (Fritz and Speroff 2011).

6.1 Male Infertility

Male factor infertility can account for as high as 30 % of infertility. Evaluation of male infertility is determined by a semen analysis with the goal to identify conditions that can be treated. Unfortunately, not all identified conditions that lead to male infertility can be treated and up to 50 % of males will have an idiopathic cause. Other causes of male infertility involve sperm transport (i.e., congenital absents of the vas in cystic fibrosis), gonadal disorders (i.e., cryptorchidism, Klinefelter syndrome, varicoceles, and genetic deletions or mutations), and hypothalamic-pituitary disorders. Infertility in the male can result from infections including gonorrhea, chlamydia, HIV, tuberculosis, leprosy, and mumps causing orchitis. Drugs that may cause male infertility include alkylating agents, antiandrogens, and anabolic steroids. More commonly used medications like ketoconazole and cimetidine are also linked with male infertility. Heavy use of drugs and alcohol, in particular marijuana and cocaine, will cause infertility. Other environmental exposures like febrile illness, exposure to pesticides or organic solvents, and smoking have also been associated with infertility. Additionally, chronic diseases are not uncommon in men with infertility such as cirrhosis, chronic renal insufficiency, and sickle cell disease (Fritz and Speroff 2011).

6.2 Female Infertility

The two most common causes of female factor infertility are ovulatory dysfunction, accounting for 20–40 %, and tubal or peritoneal disease, accounting for 30–40 %. These causes along with other less common causes of female infertility are discussed in further detail below (Fritz and Speroff 2011).

6.3 Ovulatory Causes of Infertility

Ovulation is a necessary means for conception. Even oligoovulation or infrequent or irregular ovulation can delay conception. Confirmatory tests for ovulation are discussed in detail below, but a menstrual history will often be enough information to determine if the patient is ovulatory. Women that are ovulatory have predictable periods at regular intervals and will often have a set of moliminal symptoms (i.e., breast tenderness) that accompanies their cycle. The most common cause of anovulation is Polycystic Ovarian Syndrome or PCOS. PCOS is a condition characterized by an increased number of cysts on the ovaries, hyperandrogenism often characterized by acne and hirsutism, and oligo or anovulation.

6.4 Structural Causes of Infertility

6.4.1 Tubal

Tubal patency is necessary for conception as fertilization of the egg and sperm occurs in the fallopian tube. The two main causes of tubal occlusion are the result of a prior infection and endometriosis. Infectious causes of tubal occlusion include pelvic inflammatory disease (PID) and a prior infection with gonorrhea and/or chlamydia. Infertility increases with each occurrence of acute pelvic inflammatory disease and those with a history of three episodes of acute PID can

have and infertility rate up to 75 %. Other causes of tubal occlusion include abdominal adhesive disease and prior ectopic pregnancy (Fritz and Speroff 2011).

6.4.2 Uterine

Uterine abnormalities are an infrequent cause of infertility, but should still be considered in an infertility evaluation. The most common uterine causes of infertility include fibroids, polyps, adhesions, and developmental anomalies. All of these conditions interfere with implantation and may increase the risk of miscarriage as well. Fibroids are monoclonal growths that occur commonly in women. Up to 40 % of women have uterine fibroids. Infertility is dependent on location of the fibroids in the uterus with submucosal having the greatest effect on infertility, especially those distorting the endometrial cavity, followed by intramural fibroids. Uterine polyps are benign pedunculated growths in the uterine cavity that often cause irregular or heavy bleeding. Uterine adhesions, or Asherman's syndrome, are the result of damage to the endometrium usually by instrumentation such as a curettage following a missed abortion or retained products of conception. Uterine developmental anomalies are exceedingly rare. The most common anomaly is a uterine septum. Others include a bicornuate uterus, a unicornuate uterus, and uterine didelphis.

6.4.3 Cervical

Infertility related to a cervical cause is rare but should be considered in women with prior treatments for cervical dysplasia. These treatments can result in cervical stenosis, and ultimately the inability of the sperm to reach the egg. Cervical stenosis can be evaluated in the office by simply passing a uterine sound. In the past, a postcoital test was performed as this was thought to evaluate the interaction between the cervical mucus and sperm but this test has fallen out of favor as information obtained from the results of the test did not change pregnancy outcomes and the test was largely inconvenient and embarrassing for patients.

6.4.4 Endometriosis

Endometriosis is a chronic disease in which there is uterine tissue outside the uterus, predominately in the pelvis. This tissue acts as normal endometrial tissues and responds to the hormonal changes of the cycle. As a result, endometriosis can cause pain and infertility. Around 25–50 % of infertile women have endometriosis and 30–50 % of women with endometriosis have issues with infertility. Caucasian women are more likely to have endometriosis and risk factors include smoking, alcohol use, and a low body mass index. Although endometriosis affects fertility, the mechanism in which it does so is unclear. Several mechanisms have been proposed but none have been proven indefinitely. Some mechanisms include a distorted pelvic anatomy, systemic and local inflammation, and decreased uterotubal transport capacity (Committee Opinion: Endometriosis and Infertility 2012a).

6.5 Unexplained Infertility

Unexplained infertility is a diagnosis of exclusion and accounts for up to 30 % of cases of infertility. All other explanations of infertility must first be ruled out prior to making this diagnosis. This includes proof of ovulation, proof of a normal uterine cavity and patent fallopian tubes, and a normal semen analysis. It is difficult to say if the cause of decreased fecundity in couples with unexplained infertility is due to a cause we have not identified or if the cause is one of the known explanations for infertility and it is just not picked up by the diagnostic tests performed. Unexplained infertility is more common in women >35 years old suggesting that age plays a role. Prognosis for a couple with unexplained infertility is poor without treatment. Without treatment, the conception rate for a couple with unexplained infertility is only about 20 % after 5 years (Fritz and Speroff 2011).

7 Diagnosis

The diagnosis of infertility is made when a couple has failed to achieve a successful pregnancy by 12 months of timed unprotected intercourse or therapeutic donor insemination. There are certain circumstances that warrant earlier evaluation. The American Society for Reproductive Medicine recommends evaluation of infertility for women ≥35 after 6 months of attempted conception and immediately for women ≥40 (Committee Opinion No. 589 2014a).

7.1 History and Physical Exam

A large proportion of the etiology of infertility can be determined from the couple's history. The interview with the infertile couple generally takes place with both the male and female present for the interview. Below are questions that may be of benefit to determine the cause of infertility.

QUESTIONS FOR BOTH MALE AND FEMALE

Do you have any medical problems? (Endometriosis, polycystic ovarian syndrome, thyroid disease for females, cystic fibrosis, Klinefelter syndrome for males)

Have you had any surgeries? (Previous laparoscopy for endometriosis for females, any testicular surgery for males)

Are you taking any medications? (Chemotherapy, antiandrogens, birth control, ketoconazole, cimetidine)

Do you smoke, drink alcohol, or use illicit drugs?

Do you have any family history of birth defects or mental retardation? (May indicate genetic causes of infertility)

Have you been pregnant before/have you fathered a child before? (Determine gravity and parity, and determine primary or secondary infertility, and male or female infertility)

How long have you been trying to conceive?

How often are you having intercourse?

Have you had any previous infertility work up?

Have you had infertility issues in a previous relationship?

Do you have any history of sexually transmitted infections? (PID, gonorrhea, chlamydia)

QUESTIONS SPECIFIC TO THE FEMALE

At what age did you start your periods?

How long are your cycles? Are they regular? (May indicate ovulatory dysfunction, regular cycle is 21–35 days)

Do you have painful periods? (Dysmenorrhea many suggest endometriosis)

Do you have pain with intercourse? (Dyspareunia may suggest endometriosis)

Have you had any abnormal pap smears? What was the treatment? (May indicate cervical stenosis if prior excisional procedure or cryoablation)

Do you know when you will menstruate? (Moliminal symptoms suggest ovulation)

Have you had any miscarriages?

Do you have a family history of early menopause?

What have you used for birth control in the past? (Depo Provera has a longer time to conception after discontinuation)

QUESTIONS SPECIFIC TO THE MALE

Have you had a semen analysis before?

What do you do for work? (Environmental exposures: pesticides or organic solvents, truck driving may cause infertility)

7.2 Physical Exam

The physical exam should include vitals, a body mass index, a thyroid exam, a breast exam with evaluation for galactorrhea, evaluation of excess androgens (hirsutism and acne), and a pelvic exam. The pelvic exam should include evaluation of cervical abnormalities and cervical or vaginal discharge, uterine contour, size and mobility, adnexal tenderness or fullness, and an evaluation of the cul-de-sac. Findings on exam that may point to endometriosis may include a fixed uterus, an adnexal mass (endometrioma), nodularity of the uterosacral ligaments, and overall tenderness on exam.

7.3 Diagnostic Tests

Diagnostic evaluation should be cost efficient and timely. Tests that are both minimally invasive and high yield should be performed first. Diagnostic tests should also focus on the most likely cause of infertility based on the couple's interview. Below is a discussion on diagnostic tests that are used to evaluate the most common causes of infertility.

7.3.1 Diagnostic Test for Ovulation Confirmation

Although a good menstrual history is a good evaluation tool for ovulation, there are several tests to confirm ovulation.

Ovulation Prediction Kits

Ovulation predictor kits are available over the counter and can be purchased at most drug stores. These kits detect the luteinizing hormone (LH) surge as LH is excreted in urine. Patients are instructed to urinate on the test sticks, similar to a pregnancy test, in the afternoon or evening as the LH surge typically starts in the morning and cannot be detected by the test until a threshold has been reached. As the LH surge proceeds ovulation by 1–2 days, the test is useful in determining the time of greatest fertility in the cycle which is usually the day of the LH surge and the following day. The patient is instructed to have intercourse based on the positive result. Ovulation predictor kits not only confirm ovulation but have many other benefits. Ovulation predictor kits allow for women to be involved in their treatment and care, it is a relatively quick and easy test, and it allows for timed intercourse for couples who have infrequent intercourse. There are drawbacks to ovulation predictor kits as well. They can be expensive for some patients; depending on the brand, they can be difficult for the patient to interpret, and there is a chance of false positive and false negative test results (Committee Opinion: Diagnostic Evaluation of the Infertile Female 2015a).

Basal Body Temperature Charts

Basal body temperature (BBT) record is an inexpensive way to determine when ovulation occurs. The patient is instructed to take her temperature every morning prior to getting out of bed and document the result on graph paper. With the rise in progesterone following ovulation, the BBT will increase about 0.4 to 0.8° Fahrenheit and this can be appreciated on the chart. Ovulation usually occurs 4–5 days prior to the temperature change. Unfortunately the patient will not be aware that ovulation has occurred until a full cycle of temperatures are obtained. For this reason, the BBT charts are best used when data can be reviewed over several months. Patients should be instructed to have every other day intercourse for 7 days prior to the change in body temperature based cycle trends. Although this method is inexpensive for patients, it is tedious and takes time. For this reason, the American Society of Reproductive Medicine no longer recommends this evaluation as the best or preferred method to evaluate ovulatory function (Fritz and Speroff 2011 and Committee Opinion: Diagnostic Evaluation of the Infertile Female 2015a) (Fig. 1).

7.4 Serum Progesterone

Serum progesterone levels have proven to be a reliable evaluation of ovulation. In the past, this level was typically drawn on cycle day 21. As cycle lengths vary greatly among women, this may be accurate for women with 28 day cycles, but will not be useful for women with shorter or longer cycles. For this reason, The American Society of Reproductive Medicine recommends that serum progesterone be drawn 1 week prior to the day of anticipated menses. A serum value >3 indicates ovulation has occurred. As a review, serum progesterone is low in the follicular phase and increases steadily after ovulation and again is low during menses. A serum progesterone level is the most commonly used test for confirmation of ovulation as it is easy and a reliable test (Fig. 2).

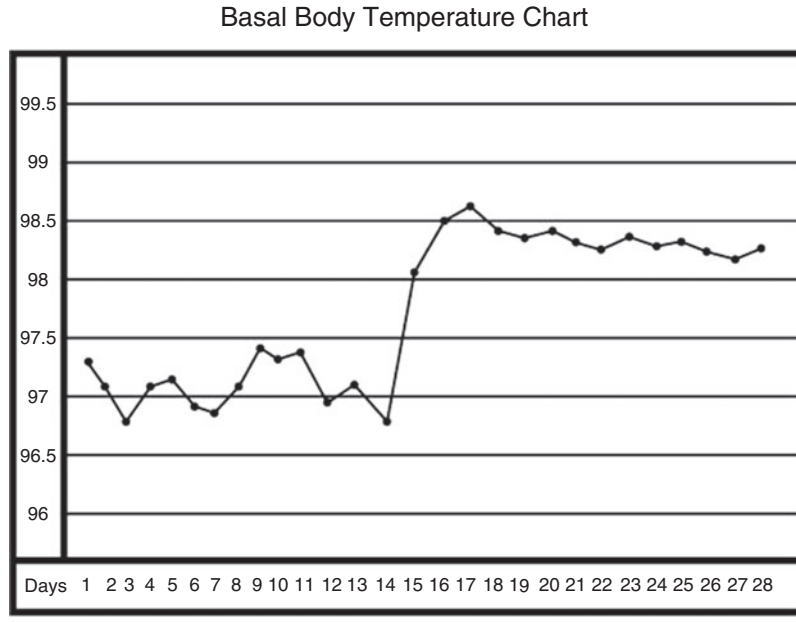

Fig. 1 Basal body temperature chart

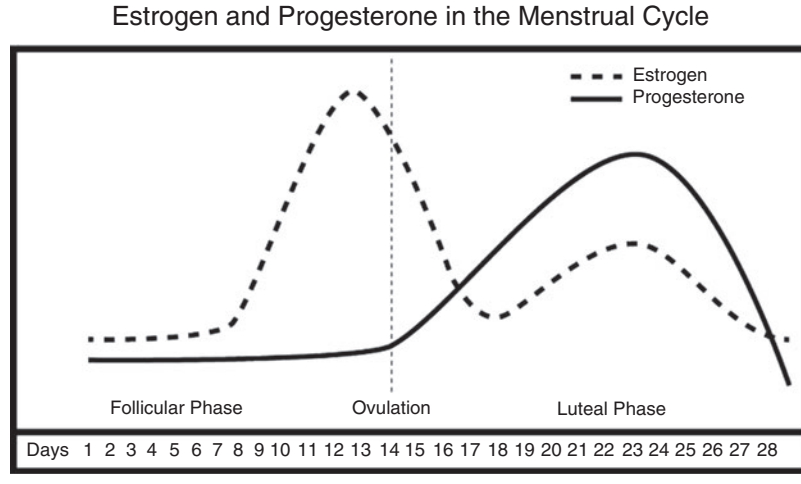

Fig. 2 Progesterone in the menstrual cycle

7.5 Diagnostic Tests for Tubal Patency

7.5.1 Hysterosalpingogram

A hysterosalpingogram or HSG is a procedure performed in the radiology department in which contrast is pushed into the uterine cavity. Fluoroscopic images are taken to determine if the dye introduced was able to exit the tubes which by confirming tubal patency. This procedure does not require any anesthesia or sedation and can be performed by either a trained radiologist or gynecologist. An acorn manipulator or a small tube is passed though the cervix to the internal os. Approximately 10 cc of contrast is all that is needed to obtain images. As the contrast is introduced, the patient may have mild discomfort but overall this procedure is tolerated quite well. Typically three images are obtained and there is minimal radiation exposure. An image is obtained

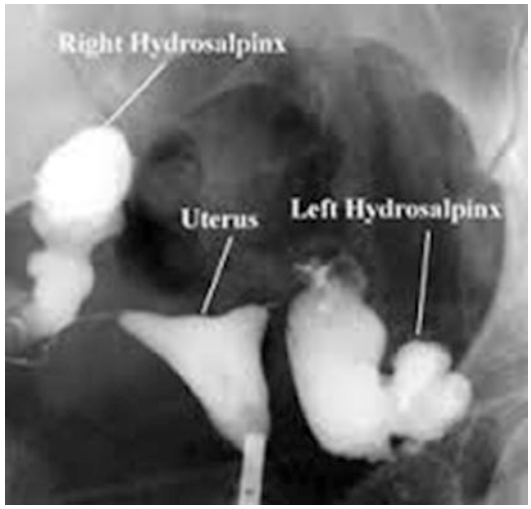

Fig. 3 HSG picture showing hydrosalpinx

when the dye fills the uterine cavity to document the shape and filling of the cavity. Additional pictures are taken as the dye fills the tubes and when the dye spills into the peritoneal cavity. When the dye enters the peritoneal cavity, it disperses creating a cloud like image on fluoroscopy, see below. If one or both of the tubes are occluded, this image will not be visualized. Either hydrosalpinx, or a dilation of the tube, and salpingitis isthmica nodosa, or thickening of the tube, can be appreciated on HSG. Both of these conditions are associated with infertility. Occasionally, one or both tubes can spasm during the procedure preventing the dye from passing though the tubes and giving the impression that one or both tubes are occluded. To prevent spasm, it is best to introduce the dye slowly. Atropine can also be given prior to the procedure for prevention. Nonsteroidal anti-inflammatory medications are frequently given prior to, or just following the procedure. The American Congress of Obstetricians and Gynecologists or ACOG recommends giving a 5 day course of doxycycline 100 mg BID if dilated tubes are seen on HSG or this course can be completed before the procedure in patients with a history of PID to prevent post procedure PID. If a patient has not had a history of PID, the procedure can be completed without the use of antibiotics (Practice Bulletin No. 104 2009) (Fig. 3).

7.6 Chromotubation

Chromotubation is similar to an HSG but is done at the time of surgery, most commonly at the time of a diagnostic laparoscopy. An acorn manipulator is placed though the cervix during an open or laparoscopic case. A blue dye, usually indigo carmine, is pushed into the uterine cavity through the acorn manipulator. The surgeon then watches the fimbriae of the fallopian tubes for spillage of the blue dye, confirming patency. If no leaking of blue dye is observed, then the tube is occluded. Antibiotic recommendations by ACOG are the same for chromotubation as for HSG. Although chromotubation requires general anesthesia, it does have some benefits over HSG. Chromotubation is a more accurate test for tubal patency and as it is more invasive, lends itself to correction of identifiable problems. For example, tubal adhesions and tubal phimosis, an occlusion near the fimbriae, can be corrected at the time of surgery (Fig. 4).

7.6.1 Diagnostic Tests to Evaluate the Uterine Cavity

Both a transvaginal ultrasound and HSG are common first line diagnostic tests to evaluate the uterine cavity. The diagnostic test of choice for evaluation of the endometrial cavity can be tailored to the patient's history. If the patient has a history of fibroids, menorrhagia, or a family history of fibroids, a transvaginal ultrasound may be the most useful. If a patient has menorrhagia or intermenstrual bleeding suggesting a polyp, a sonohystogram would be the preferred method of evaluation. Below is a discussion of the different modalities available to evaluate the uterine cavity.

Transvaginal Ultrasound

Transvaginal ultrasound (TVUS) is a quick and easy way to evaluate the uterus. It can easily identify uterine fibroids and can detect some uterine anomalies but MRI or 3-D ultrasound is usually best for detecting complex anomalies. Transvaginal ultrasound also has the benefit of evaluating the ovaries and can be done in the office. Although it will likely identify fibroids

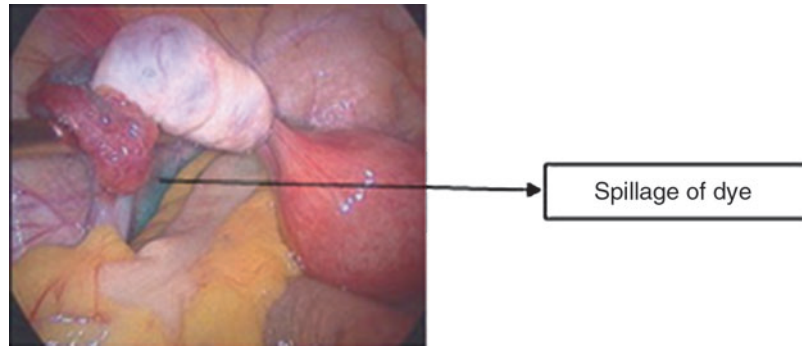

Fig. 4 LSC image of chromotubation demonstrating tubal spillage

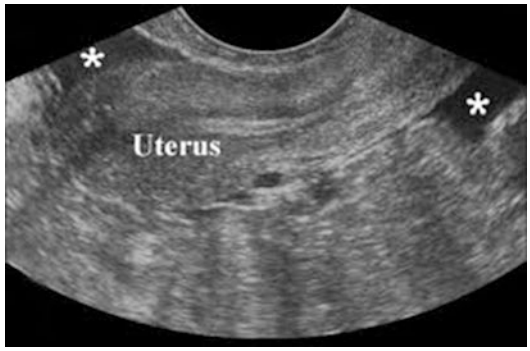

Fig. 5

impinging on the uterine cavity, it is a poor detector of uterine polyps. As the uterine cavity is not expanded during a TVUS, polyps and adhesions can easily be missed. TVUS may also be helpful in distinguishing between a septate uterus and a bicornuate uterus by examining the shape of the fundus as a septate uterus will have a normal fundus and a bicornuate uterus will have a heart shaped fundus (Fig. 5).

7.7 Hysterosalpingogram

Hysterosalpingogram or HSG can also be used to evaluate the uterine cavity. The procedure is described above, but the filling of the uterine cavity with contrast allows for evaluation of the uterine shape. An HSG can identify polyps, fibroids that protrude into the endometrial cavity, and uterine adhesions (Asherman's syndrome). An HSG can also be helpful in diagnosing uterine

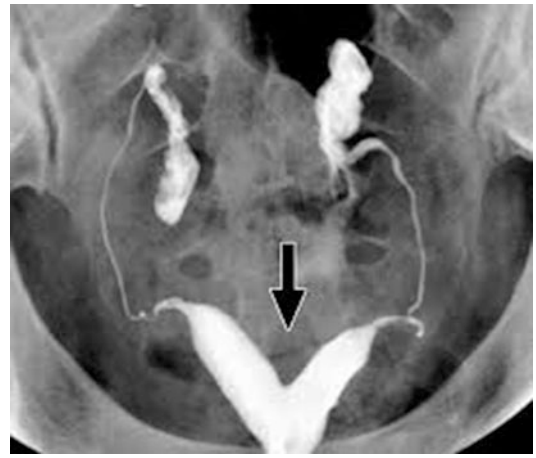

Fig. 6 HSG demonstrating uterine anomaly

anomalies, if the usual triangle shape of the uterine cavity is misshapen. If a bicornuate or septate uterus is suspected on HSG, again, a TVUS will be needed to determine the shape of the uterine fundus. Although an HSG can identify polyps and fibroids, it has a relatively low sensitivity and positive predictive value, 50 % and 30 %, respectively (Committee Opinion: Diagnostic Evaluation of the Infertile Female 2015a) (Fig. 6).

7.7.1 Sonohystogram

A sonohystogram is an in-office procedure to evaluate the endometrial cavity. Similar to an HSG, the cervix is cannulated and saline is introduced into the endometrial cavity. A simultaneous TVUS is performed. The saline distends the normally compressed endometrial cavity and the saline appears dark, or anechoic, allowing the

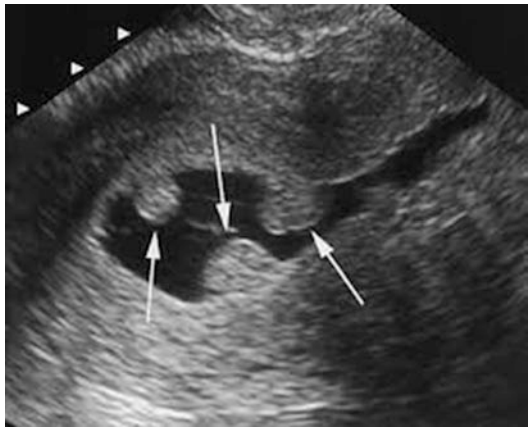

Fig. 7 Sonohystogram demonstrating endometrial polyps

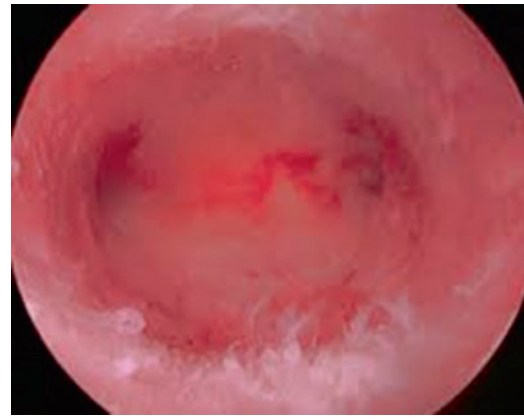

Fig. 8 Image of normal endometrial cavity

physician to see any abnormalities in the cavity including polyps, fibroids, and adhesions. Compared to an HSG and a TVUS, a sonohystogram is a better test for evaluating the endometrial cavity with a positive predictive value of >90 %. It is also useful in identifying uterine anomalies, but once again other imaging like an MRI or 3-D TVUS may be needed. ACOG does not recommend routine antibiotic prophylaxis for this procedure but does recommend considering treatment based on the patient's personal history of PID (Practice Bulletin No. 104 2009) (Fig. 7).

7.8 Hysteroscopy

Hysteroscopy is the most definite way to evaluate abnormalities in the endometrial cavity. It is a minor surgical procedure requiring general anesthesia in which the cervix is dilated and a camera is introduced through the cervix into the endometrial cavity and a survey of the cavity is performed. Fibroids, polyps, and adhesions are easily seen by the surgeon. The benefit of hysteroscopy over the other methods is that it allows for correction of the abnormality. Fibroids, polyps, and adhesions can be removed at that the time of the procedure. As a hysteroscopy is an invasive procedure, generally, an HSG, TVUS, or sonohystogram is performed first followed by a hysteroscopy to correct the findings on the preliminary diagnostic tests. In the recent past,

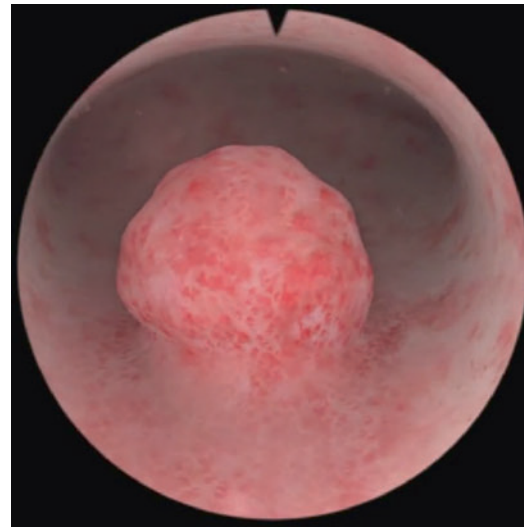

Fig. 9 Image of polyp on hysteroscopy

hysteroscopy has become a common in-office procedure. As there is no need for general anesthesia or even sedation, this has become an increasingly popular trend. In-office hysteroscopy may become a more common first-line evaluation of the endometrial cavity in the infertile patient in years to come. As the postprocedure PID rate is low with hysteroscopy, ACOG does not recommend prophylactic antibiotic but antibiotics may certainly be considered based on the patient's history of PID (Practice Bulletin No. 104 2009) (Figs. 8 and 9).

7.9 Tests for Ovarian Reserve

As discussed previously, ovarian function, and therefore the fecundity rate decreases with increasing age. There are several indications to investigate ovarian reserve. These include age ≥35, a family history of early menopause, any history of ovarian surgery, a history of chemotherapy or pelvic radiation, a history of a unilateral oophorectomy, unexplained infertility, or plans to initiate artificial reproductive technology (Committee Opinion: Diagnostic Evaluation of the Infertile Female). The following tests are not diagnostic in nature, they simply give a prognosis. An important point to discuss with patients is that just because a lab in abnormal does not definitively mean that conception is impossible. These tests are also useful in determining appropriate treatments and success rates with artificial reproductive therapies.

7.9.1 Serum Follicle Stimulating Hormone

Serum follicle stimulating hormone (FSH) and estradiol (E2) can be obtained on cycle day 2–4. An elevated FSH is one of the first signs of decreased ovarian reserve. Although different assays may have different cut-off values, a result >10 IU/L is generally considered elevated. As there is some fluctuation in FSH between cycles so this test can be repeated. Consistently elevated FSH levels often confer a poor prognosis for conception.

Serum estradiol is drawn at the same time as the FSH and levels are only useful to interpret the result of the FSH level. With reproductive aging, estradiol levels increase earlier in the cycle. An elevated estradiol level, >60–80 pg/mL, may suggest that the patient is in the beginnings of ovarian aging. Estradiol is not useful alone and even when used with FSH is a poor prognostic tool for conception (Committee Opinion: Testing and Interpreting Measures of Ovarian Reserve 2015c).

7.9.2 Antral Follicle Count

The antral follicle count or AFC is a count of ovarian follicles by TVUS measured in the follicular phase. It is a total count of follicles measuring anywhere from 2 to 10 mm in mean diameter from both ovaries. Follicles with a mean diameter of one or less are not counted in the AFC. A value of less than 3–6 is considered low. It is important to note that polycystic ovarian syndrome or PCOS will increase the AFC and combined oral contraceptive pills can decrease the AFC (Committee Opinion: Testing and Interpreting Measures of Ovarian Reserve 2015c).

7.9.3 Antimullerian Hormone

Antimullerian hormone or AMH is produced by the granulosa cells in the antral follicles. The level of AMH produced by the granulosa cells decreases overtime until it ceases at menopause. It is a measure of the pool of remaining follicles; therefore, a low AMH is concerning for a decreased ovarian reserve. Unlike FSH, serum AMH can be drawn anytime during the cycle. AMH can be affected by exogenous estrogens including OCPs and even obesity. Women with PCOS have an elevated AMH, up to a threefold increase from the normal population. Generally, values less than one confer a poor prognosis for conception (Committee Opinion: Diagnostic Evaluation of the Infertile Female 2015a).

7.10 Other Laboratory Tests

Thyroid stimulating hormone or TSH and a prolactin should be ordered in women with oligo or amenorrhea as this may be a contributing factor to the patient's infertility. Both thyroid disorders and hyperprolactinemia are treatable conditions. If the patient has hirsutism along with anovulation, a testosterone, DHEA-S, and a 17-hydroxyprogesterone should also be ordered.

7.11 Diagnostic Tests for Evaluation of Male Infertility

7.11.1 Semen Analysis

The semen analysis is the most important evaluation for male infertility. The specimen can be collected at home or in the office but if the specimen is collected at home, it needs to not only be

kept at room temperature but also be evaluated within 1 h of ejaculation. The patient is also instructed to abstain for 2–5 days prior to collection. The volume, pH, concentration, total sperm number, motility, and morphology are then analyzed. The table below has normal reference ranges. Azoospermia is the absence of sperm, oligospermia is a concentration of <20 million/mL, and athenospermia refers to decreased sperm motility. If there is any abnormality in the semen analysis, the patient should be referred to an urologist.

Semen Characteristics	
Volume (mL)	≥1.5
Sperm count (106/mL)	≥15
Total sperm count (106)	≥39
Total motility (%)	≥40
Morphology (%)	≥4
Vitality (%)	≥58
Leukocyte count (106/mL)	<1.0

8 Treatments

Treatments for infertility depend on the cause. For example, if a couple is having intercourse once a month, increasing the frequency of intercourse around the time of ovulation will increase the chance of pregnancy. If the female has a diagnosis of endometriosis, a laparoscopic procedure to fulgurate or burn the endometrial implants may increase the chance of pregnancy. Before initiation of treatment, both the male and female should optimize their health. This may mean smoking cessation, decreasing caffeine and alcohol intake, and in some cases, weight loss. Remember that all women attempting conception should be taking a prenatal vitamin and folic acid supplementation.

8.1 Optimizing the Window of Fertility

Although patients may understand how to get pregnant, they may not fully understand how to optimize their chances. The couple's history may reveal that the timing and frequency of intercourse may be the cause of their infertility. For a couple having infrequent intercourse especially if it is not timed around ovulation, simply educating the couple can increase their chances of conception. This information is also useful for any couple trying to conceive.

The time in which the chance of conception is the greatest is called the "fertile window." This window is the 6 days prior to ovulation so intercourse should be most frequent during this time. As mentioned previously, the timing of ovulation can be determined by several methods including BBT charts, OPK, and cervical mucus. Cervical mucus becomes clear and slippery around the time of ovulation. A simple way to determine the "fertile window" for women with regular periods is to establish cycle length with a menstrual chart or diary. Ovulation occurs 14 days prior to menses as the luteal phase is usually consistent. For a woman with a regular cycle, the time of ovulation can easily be predicted based on cycle length.

Recommendations for frequency of intercourse should be every 1–2 days during the "fertile window." There is only a small increase in the rate of conception from every day to every other day so if daily intercourse is difficult or stressful for the couple, this should not be advised. Several myths exist about intercourse that should be dissipated. There is no position that increases the chance of conception and there is no length of time that the female needs to be supine after intercourse. Female orgasm does facilitate sperm transport but does not change the rate of conception (Committee Opinion: Optimizing Natural Fertility 2008).

8.2 Treatment for Ovulation Dysfunction: Ovulation Induction

Clomiphene citrate or clomid is an estrogen agonist and antagonist. It works by competitively binding estrogen receptors in the thalamus and as it remains in place for an extended period of time, it depletes the body's estrogen concentration at the hypothalamic level. As the body perceives low levels of estrogen, gonadotropin-releasing

hormone or GnRH is released which in turn stimulates pituitary release of follicle stimulating hormone or FSH which promotes follicular growth and maturation. The dosing of clomiphene citrate is weight dependent but the goal is to treat the patient with the lowest dose that induces ovulation. The starting dose is generally 50 mg and is increased by 50 mg until ovulation has occurred. The dose should not be increased just because conception does not occur. The FDA has not approved clomiphene citrate for ovulation induction >100 mg. Around 50 % of women will ovulate with just 50 mg and an additional 22 % will ovulate with 100 mg. Clomiphene citrate is administered for 5 consecutive days starting on any day from cycle day 2–5 following natural menses or progesterone induced menses. There are a few side effects of clomiphene citrate and it is generally well tolerated. The most common side effect is mood swings which occur in the majority of patients, 64–78 %. Other side effects which are far less common include breast tenderness, pelvic pain, and nausea. There are reports of optic neuritis with clomiphene citrate use so if the patient reports any visual disturbances, clomiphene citrate should be stopped and another form of ovulation induction should be considered. There is always a risk of multiple gestation with clomiphene citrate, around 8 %, but higher order multiples are rare. Clomiphene citrate is category X in pregnancy so should not be used if pregnancy is suspected and a pregnancy test should be considered before use. If pregnancy is not achieved by 3–6 cycles, other treatments should be considered as pregnancy is most likely to occur in that time period (Committee Opinion: Use of Clomiphene Citrate in Infertile Women 2013).

Aromatase inhibitors are used to treat breast cancer but have been used for ovulation induction as well. The most commonly used drug is letrazole or Fumara. This medication is not approved by the FDA for infertility use. In 2005, the manufacturer of letrazole released a warning regarding its use in premenopausal women. In early studies, the data suggested that women using letrazole had infants with higher rates of cardiac and bone malformations but these results have not been reproduced in subsequent studies. Aromatase inhibitors block the enzyme aromatase that converts androgens to estrogens. With decreased levels of estrogen, the body compensates with increased release of FSH. Letrazole is typically dosed at 2.5 mg or 5 mg in a fashion similar to clomiphene citrate, five consecutive days starting anytime on cycle day 2–7. Aromatase inhibitors have been shown to be effective in women who do not ovulate with clomiphene citrate. Studies suggest that aromatase inhibitors are as effective as clomiphene citrate for a first-line treatment of anovulation. Additionally, there is a lower rate of multiples with aromatase inhibitors when compared to clomiphene citrate.

Use of exogenous gonadotropins should be reserved for those that are trained in administration. The use of gonadotropins require injection of the medication, serial ultrasounds every 1–2 days, and serial serum estradiol levels. Gonadotropins are expensive, have a higher risk of ovarian hyperstimulation syndrome, and carry a high risk of multiples, upwards of 15 % overall. For these reasons, administration of these medications should be from a provider experienced in their use. Gonadotropins are reserved for patients with hypogonadotrophic hypogonadism, those that do not ovulate with clomiphene citrate, and those with unexplained infertility. As the dosing for every patient is individualized and changes in dosing are based on ultrasound and estradiol results, there are many regimens for dosing. Once the dominant follicle becomes large enough, usually 20 mm in mean diameter, ovulation is induced with an injection of hCG which mimics the LH surge. Pregnancy rates are high for women with hypogonadotrophic hypogonadism, up to 90 % by 6 months, but much lower for patients that are clomiphene citrate resistant with cumulative conception rates between 30 % and 60 %. Additionally, there is a higher rate of miscarriage with gonadotropin use (Fritz and Speroff 2011).

8.3 Treatment for Decreased Ovarian Reserve

Depending on the severity of ovarian aging, using the patient's own eggs may not be a possibility as

the ovaries may not respond to exogenous gonadotropins. If a day 3 FSH is greater than 15 IU/L, exogenous gonadotropins will not induce a response. In these situations, and others in which ovarian function is compromised, other therapies must be considered, such as egg donation or gestational surrogacy, also known as third party reproduction (Hoffman et al. 2012).

8.3.1 Egg Donation

Egg donation refers to a woman that donates her egg to a recipient that is unable to conceive. Egg donation is traditionally reserved for women that are in early menopause, those that have surgical removal of their ovaries, or those that have a genetic condition that could be passed on to their offspring. Egg donors can be anonymous, known to the recipient, or some couples may offer to donate their leftover eggs after an IVF cycle. The donor is extensively screened prior to donation with a medical history, a mental health evaluation, test for infectious diseases, and genetic testing. Eggs are obtained through an in vitro fertilization (IVF) process; see below for a detailed explanation of IVF. Essentially, the donor receives exogenous gonadotropins and when the follicles are mature, a procedure is preformed to retrieve the eggs. The donor eggs are fertilized with the recipient's partner's sperm to make an embryo. In the meantime, the egg recipient receives estrogen and progesterone to prepare the endometrium for embryo transfer into the uterus. The live birth rate for donor egg programs is around 55 %. There is an increased risk of multiples with egg donation, upwards of 40 % (Third Party Reproduction 2012).

8.3.2 Gestational Surrogate

A gestational surrogate is someone who carries the pregnancy for a woman who cannot do so. Reasons for a gestational carrier include women without a uterus or those with certain types of uterine malformations, those with severe uterine adhesions that cannot be corrected, or those with a medical condition that is contraindicated in pregnancy. There are two types of gestational surrogacy, traditional surrogacy and gestational carrier. Traditional surrogacy is when the surrogate is inseminated with the sperm of the couple seeking surrogacy and a gestation carrier is when the surrogate is inseminated with an embryo from the couple. A similar medical work-up and evaluation for egg donation is performed for the surrogate. With both egg donation and gestational surrogacy, many legal questions may arise. As laws differ from state to state regarding third party reproduction, patients should be advised to seek legal counsel prior to proceeding (Third Party Reproduction 2012).

8.4 Treatment for Male Infertility

The treatment for male infertility depends not only on the cause but on the severity of the sperm quantity and quality. In cases of aspermia secondary to anejaculation, the patient may benefit from counseling if the cause is psychogenic. They may benefit from sildenafil if erectile dysfunction is the cause and even vibratory stimulation. If the patient has a spinal cord injury they may require electroejactulation to acquire sperm. If the patient has retrograde ejaculation, an alpha adrenergic will be of benefit as it will promote bladder neck closure. For those with hypospermia secondary to an obstruction, surgery may be of benefit to resect the narrowing. For those patients with congenital absence of the vas deferens, associated with cystic fibrosis, a testicular sperm extraction (TESE) can be performed. Intrauterine inseminations and assisted reproductive technologies can be offered for male infertility as well. If assisted reproductive technology is used for male infertility, intracytoplasmic sperm injection (ICSI) should be utilized.

A varicocele is a dilation of the scrotal veins, typically on the left, and present in 40 % of males with infertility. There is evidence to suggest that varicoceles cause dysfunctional spermatogenesis but evidence as to whether repair improves conception rates has been controversial. Although most studies demonstrate improvement in pregnancy rates following repair, these studies are small in size and poor in quality. The American Society of Reproductive Medicine recommends offering treatment of varicoceles to men when all

or most of the following are present: a palpable varicocele on exam, known infertility, a female with a normal fertility evaluation or a treatable cause of infertility, and an abnormal semen analysis. Options other than surgical repair of a varicocele are intrauterine inseminations or in vitro fertilization with intracytoplasmic sperm injection (Committee Opinion: Report on Varicocele and Infertility 2014b).

8.5 Treatment for Unexplained Infertility

By definition, the cause for unexplained infertility is unknown so it can be difficult to know which treatment is appropriate for each couple. Treatment options include ovulation induction, intrauterine inseminations, gonadotropins, in vitro fertilization, or even expectant management if the female is young and the couple so desires. When used alone, intrauterine inseminations increased conception rates in the unexplained infertile couple, although only by a small amount, 4 % versus 2 %. When clomiphene citrate was used alone, the effects on conception were also significant but small. There is currently not enough data to definitively comment on the conception rates with clomiphene citrate and IUI as studies are lacking. Gonadotropins used with IUI have proven to be effective treatment for unexplained infertility. The pregnancy rate is around 8 % when gonadotropins are used alone and around 18 % when IUI is added for couples with unexplained infertility. ART has the highest success rate with a live birth rate of around 30 % for couples with unexplained infertility. When considering treatment options, it is important to consider the risks of multiples, ovarian hyperstimulation syndrome, and the cost effectiveness of each treatment (Committee Opinion: Effectiveness and Treatment for Unexplained Infertility 2006).

8.6 Intrauterine Insemination

Intrauterine insemination or IUI is not just a treatment for one cause of infertility but can be used to treat infertility in several settings. When an IUI is preformed, a semen sample that has been prepared and washed is placed in the uterus around the time of ovulation via a small catheter to facilitate fertilization. The goal of IUI is to increase the amount of sperm that reach the egg. IUI can be used for cervical factor infertility. In this case, IUI is timed based on the LH surge detected by ovulation predictor kits. IUI can also be used for unexplained infertility and for male factor infertility alone or with the combination of clomiphene citrate or gonadotropins.

8.7 Assisted Reproductive Technology

Assisted reproductive technology refers to any treatment in which the oocyte and sperm are manipulated outside of the body. Below is a discussion on several forms of ART.

8.7.1 In Vitro Fertilization

In brief, IVF is a process in which the patient injects gonadotropins to stimulate the growth of several follicles. Once the follicles have reached maturity, a procedure called an egg retrieval is performed in which the eggs are retrieved under ultrasound guidance using a needle transvaginally on suction. This procedure is usually preformed under sedation in the office. The aspirated ova are then combined with the partner's sperm in vitro. The embryo, and sometimes more than one embryo, is transferred into the uterus under ultrasound guidance. ASRM has a committee opinion for the number of embryos to transfer based on age of the female and fertility prognosis.

IVF is indicated for infertility for which there is no treatment, male factor infertility, severe tubal disease or severe endometriosis, infertility in which there are multiple causes, unexplained infertility, or when other treatments fail. Risks of IVF include multiple gestations and the associated pregnancy complications. In 2006, 30 % of live births in the US due to ART were multiples (Committee Opinion; Multiple Gestation Associated with Infertility Therapy 2012b). Another risk of IVF is ovarian hyperstimulation syndrome. Ovarian hyperstimulation syndrome is a clinical

diagnosis characterized by abdominal pain, ascites, oliguria, hemoconcentration, and thromboembolism. The primary treatment is supportive care and paracentesis may be required. Pregnancies conceived by IVF also carry a higher risk of preeclampsia, placenta previa, and abruption.

Of all the treatments for infertility, IVF has the highest success rate per cycle. Around 70 % of all, ART are IVF and most use fresh oocytes. Sixty-three percent of these cycles use ICSI and around 35 % resulted in pregnancy. If a frozen embryo was used, live birth rate was around 30 % (Fritz and Speroff 2011).

A discussion of IVF is not complete without discussing cost effectiveness of this treatment. IVF is an expensive treatment and can become quite a financial burden to the couple especially after several cycles. The estimated average cost of an IVF cycle is around $12,500 (Resolve 2006).

8.7.2 Intracytoplasmic Sperm Injection

Intracytoplasmic injection or ICSI is a process used in IVF used for male factor infertility. A single sperm is injected past the zona pellucida and oocyte cell membrane. Pregnancy rates with ICSI are comparable to those IVF cycles in which ICSI is not indicated. This procedure has made pregnancy possible for men with azoospermia or severe male factor infertility a possibility.

8.7.3 Gamete Intrafallopian Transfer and Zygote Intrafallopian Transfer

Gamete Intrafallopian transfer or GIFT is similar to IVF but once the oocytes are retrieved, they are laparoscopically injected into the oviduct along with sperm. This was a popular treatment in the 1980s but has fallen out of favor with the increasing advances in IVF. This procedure is now preformed for those couples who have religious concerns about fertilization that does not occur in vivo.

Zygote intrafallopian transfer or ZIFT is also similar to IVF but the zygote is not transferred back into the uterine cavity but rather into the fallopian tube at the time of laparoscopy. ZIFT is not a common procedure and is generally reserved for those patients that a transcervical transfer is not possible (Hoffman et al. 2012).

8.8 Surgical Treatments

8.8.1 Laparoscopic Treatment of Endometriosis

For mild endometriosis, evidence suggests that laparoscopic ablation of endometrial implants improves conceptions rates. This improvement is small but significant. For those with severe disease, surgical ablation of endometrial implants and restoring anatomy improves fertility. If the patient has an endometrioma, the cyst wall should be removed as this will not only increase the pregnancy rate but also decrease the recurrence. Additional surgery for ablation of implants does not improve fertility (Committee Opinion: Endometriosis and Infertility 2012a).

8.8.2 Tubal Reversal

Tubal reversal is an option for patients that have had a tubal ligation. IVF is another viable option for patients with a tubal ligation. It is difficult to compare these two treatments as pregnancy rates for tubal reversal are reported as a cumulative rate and pregnancy rates for IVF are reported per cycle. There are pros and cons to each treatment and these should be discussed with the patient. The benefits of a tubal reversal are that unlike IVF, it will be beneficial for more than one cycle and will likely be less costly. Although there are risks associated with surgery, the risks associated with IVF are avoided. The cumulative pregnancy rate after 2 year when a microsurgery technique was used is around 90 % (Committee Opinion: Role of Tubal Surgery in the Era of Assisted Reproductive Technology 2012c).

9 Conclusion

Infertility is not just a diagnosis; it is a disease that requires a comprehensive evaluation and treatment specific to the couples' cause of infertility. With more couples not only delaying childbearing, but more patients aware of treatment for

infertility, the amount of couples seen for infertility concerns in the office will likely continue to be on the rise. For these reasons, the practitioner should be aware of important pieces of the history, appropriate lab work, and diagnostic tests.

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Management of the Symptoms of Perimenopause

Courtney Ketch, Elizabeth Weedin, and BreeAnna Gibson

Contents

Abstract

The term "perimenopause" refers to the time period when women transition into menopause. Many see the beginning of this transition as when a woman starts to have fluctuating menstrual cycles, which can include amenorrhea for up to 3 months. The perimenopause transition ends, and menopause begins, when a woman has had no menstrual cycles for 12 consecutive months. Many women begin to experience perimenopause in their 40s with average onset of symptoms 4 years prior to menopause. This transition time is often characterized by hormonal fluctuations and oligo-ovulation. The symptoms that can be experienced range from menstrual irregularity and hot flashes to mood changes and genitourinary symptoms. Severity and frequency of symptoms can vary widely from patient to patient. In this chapter, we will discuss some of the most common symptoms that occur during perimenopause and will explore the different options for how each of these symptoms can be managed.

Keywords

Perimenopause • Menstrual irregularity • Vasomotor symptoms • Hormone replacement • Hormonal contraception

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1 Introduction

The period of time before menopause when a woman begins to experience alterations in her menstrual cycle is known as perimenopause. While the amount of time individual women will spend in this transition period may vary, the majority will experience at least some level of symptoms associated with this phase of their life. Because the symptoms of perimenopause can greatly affect women's health and their daily life, it is important for providers to be familiar with not only the most common symptoms experienced during this time but also the most ideal and effective management strategies for these symptoms. The severity and combination of symptoms will differ from woman to woman, but this chapter will cover the symptoms that women are most likely to encounter.

2 Menstrual Irregularity

The first sign that a woman is reaching perimenopause is often identified by changes in timing, length, and intensity of the menstrual cycle. As women begin to have decreased ovulation in their later years, hormone levels begin to change. The changing hormone levels are thought to be the culprit for the alteration in menstrual flow. Women may experience increased time between their cycles, spotting, and heavier or lighter flow. The increase in irregularity of cycles can be an inconvenient and frustrating symptom for many women.

2.1 Combination Hormonal Contraception

Combination hormonal contraception can help to normalize the menstrual irregularity that occurs during the time of perimenopause. This therapy improves cycle control by stabilizing hormone levels, which allows for normalization of cycles. There are many different options for dose and route of hormonal contraception, but most can provide the benefit of regulating cycles.

Combination oral contraceptive pills (COCPs) are an easy and accessible way to assist in cycle regulation. COCPs contain both synthetic estrogen and progestin. For most women, a low-dose, monophasic contraceptive pill with 10–20 mcg ethinyl estradiol is appropriate to help control cycles; however, there are various options for pill regimen. The typical COCPs will come in a pack with 21 active pills that are hormone containing and seven placebo pills which, when taken, will allow for a withdrawal bleed to occur. There are also packs that follow a 24 active/four placebo pill cycle or, alternatively, an 84-day active pill regimen followed by seven inactive pills to allow for only four menstrual cycles in a year. All of these different regimens are effective for improved control of menstrual irregularity during perimenopause, and selection should be guided by patient preference.

There are also non-oral routes of combination hormonal contraception that can improve menstrual irregularity. A transdermal patch and intravaginal ring are available and work in a similar ways as the COCPs. Both the patch and the ring are used for 21 days and then removed for seven days to allow withdrawal of hormones and a withdrawal bleed to occur. A new patch or ring is replaced after the 7 days. Some women prefer these routes because they provide improved compliance and require less frequent administration.

When choosing combination hormonal contraception as a method for balancing menstrual irregularity, there are other benefits and risks that should be discussed with the patient. One of the major benefits of combination hormonal contraception is that it also provides a method for preventing pregnancy in perimenopausal women. While fertility is declining during the perimenopausal phase of a woman's life, it is not all together extinguished. In perimenopause, ovulation is still occurring even if it is in a more erratic pattern than earlier in a woman's life. It is important for women to understand that although remote, there still is a chance that they could become pregnant during this time.

Other benefits to COCP use include decreasing the lifetime risk of ovarian and endometrial cancers as well as increasing bone mineral density and decreasing the risk of hip fractures. It has been found that using COCPs can reduce the risk of endometrial cancer up to 50 % and that the protective benefits can persist for 10–20 years after they are discontinued. It is thought that this benefit comes from the progestin component of the pill because it helps to suppress proliferation of the endometrium (Mueck et al. 2010). Just as with endometrial cancer, COCPs decrease the chance of ovarian cancer, and the protective benefits exist for up to 30 years after discontinuation (Beral et al. 2008).

Generally speaking, bone mineral density decreases in women as they age. However, for women of older reproductive age who take COCPs into their 40s or in those who have used them for an extended period of time, this decrease in bone mineral density is blunted, which results in a reduction in risk of hip fractures (Kaunitz 2008).

Potential risks attributed to combined hormonal contraception use include increases in the risk of venothrombotic events (VTE), myocardial infarction (MI), stroke, and breast cancer. The risk of VTE markedly increases in women over 39 taking COCPs; there is almost four times the risk in women of older reproductive age as there is in adolescents on COCPs. The risk is even greater in obese women, and it has been recommended that obese women over 40 should seek methods such as progestin-only contraception or intrauterine devices for contraception and symptom management. The risk is also thought to be higher when the estrogen dose in the COCP is higher. Women with thrombophilic syndromes should avoid COCPs as treatment for their symptoms. It is important to discuss with patients if they have ever had an unprovoked VTE or if they have a family history of thrombophilic syndromes; however formal laboratory screening for these syndromes is not necessary before prescribing COCPs.

The overall risk of MI or stroke in healthy women of older reproductive age taking COCPs is very small. Some research even reports that there is no enhanced risk in these events in healthy patients without comorbidities. The increased risk of these incidents is seen more in women who smoke, who have hypertension, or who have diabetes, and thus COCPs are contraindicated in women over 35 who smoke or have diabetes. Other therapies such as progestin-only pills and IUDs are reasonable alternatives for these patients. For women with hypertension, risk is dependent on control of their hypertension.

Another potential risk that providers and patients may have questions regarding is whether or not combination hormonal contraception use causes increased risk of breast cancer. Many studies show that there is no increased risk of breast cancer in women taking COCPs at any age nor for extended periods of time. Increasing the chance of breast cancer may be a concern in women who already have a higher risk based on family history; however family history of breast cancer alone should not be seen as a contraindication for COCP use given that there is limited evidence on patients with a family history of breast cancer or BRCA mutations (Kaunitz 2008).

Ultimately, when determining if combination hormonal contraception is the right treatment for a patient, her personal medical history and risk factors for adverse events should be considered. Special attention must be paid to patient factors such as family history or personal history of diabetes, hypertension, hypercholesterolemia, thrombophilia, obesity, or smoking. The risks and benefits of treatment with hormonal contraception should be weighed for each individual patient.

2.2 Progestin-Only Methods

Providers may wonder if progestin-only forms of contraception can be used to help their patient's menstrual irregularity as well as combination hormonal contraception. Just as with combination hormonal contraception, there are different doses and forms of progestin-only contraceptive medications:

- Progestin-only pills (minipills) provide a reliable form of contraception when taken as

directed. They do not, however, provide equivalent management of irregular cycles. Women will often continue to have unpredictable cycles with this method but can see some decrease in overall flow.

- The subdermal etonogestrel implant is a method that can be kept in place for three years. Some women will experience amenorrhea with this method; however many women will experience bothersome irregular cycles, therefore not achieving the goal of cycle regulation that many perimenopausal women are seeking.
- The depot medroxyprogesterone acetate (DMPA) is a high-dose injectable progestin that suppresses ovulation and can be given every 12 weeks. Roughly half of patients that use this method will be amenorrheic after 3 months. The remaining proportion of women may not become entirely amenorrheic but typically have significantly lighter bleeding patterns.
- The levonorgestrel intrauterine device (IUD) provides contraception and a decrease in menstrual cycles for 3 or 5 years depending on which device is used. With this method, women may initially experience continued irregular light bleeding, but by 12 months 50 % of women will be amenorrheic, and the rate will continue to increase the longer the device is in place.

One of the major benefits of progestin-only methods is that they do not have the increased risk of VTE, MI, or stroke that combination hormonal methods do. The possibility of increased risk of breast cancer with progestin-only pills and DMPA injections is not completely known, but they may be similar to the risk profile seen with combination hormonal contraception. The levonorgestrel IUD has not been shown to increase the risk of breast cancer. Bone mineral density changes with the DMPA injection are one area of concern when being used in perimenopausal women because DMPA has been shown to decrease bone mineral density when used for an extended period of time. After discontinuing this method, bone mineral density appears to recover, but the increased risk of osteoporosis and fractures in older women using this method is unclear. If women have other risk factors for osteoporosis such as smoking, steroid use, or low body mass index (BMI), a different method of cycle control should likely be sought (Hardman and Gebbie 2009) (Table 1).

3 Vasomotor Symptoms

Vasomotor symptoms are the most common symptom experienced during perimenopause after onset of menstrual irregularity. Approximately 40 % of women will experience vasomotor symptoms or "hot flashes" in the early transition period, and by the later transition period, up to 80 % of women report experiencing this symptom. Hot flashes can also disrupt women's sleep habits and are described by many as "night sweats." The management of a woman's vasomotor symptoms should be based on several things: the severity and frequency of the symptoms, the patient's past medical history, coexistence of multiple symptoms, and the patient's personal choice.

3.1 Lifestyle Modifications

For mild vasomotor symptoms, behavioral changes may be adequate to manage symptoms. Keeping rooms cool, using fans, and dressing in layers are all helpful lifestyle modifications. Avoiding environmental exposures such as spicy foods and stressful situations can also help to reduce the triggering of vasomotor symptoms. There has been mixed evidence on whether regular exercise is helpful in decreasing vasomotor symptoms. Despite this, all patients should be encouraged to lead a healthy lifestyle which includes exercise, but they should know that exercise alone may not manage their perimenopausal symptoms and other treatments may need to be utilized.

Table 1 Menstrual Irregularity Management

Method	Regimen	Formulations	Additional Information
Combination Hormonal Contraception			
Combination Estrogen-Progestin Pills	21 active pills/seven placebo pills	Varying doses of estrogen and progestin	Low-dose monophasic pill with 10–20 mcg of ethinyl estradiol is appropriate for most women
	24 active/four placebo	Varying doses of estrogen and progestin	Shorter duration of a withdrawal bleed
	84 active/seven placebo	Levonorgestrel 0.15 mg, ethinyl estradiol 30 mcg	Deceases the amount of withdrawal bleeds a women will have per year
Transdermal Patch	1 patch a week × 3 weeks 1 week patch-free	Norelgestromin 150 mcg/day, Ethinyl estradiol 35 mcg/day	May be preferred by some women because it requires less frequent administration
Vaginal Ring	Place ring for 3 weeks, remove for 1 week	Etonogestrel 120 mcg/day, ethinyl estradiol 15 mcg/day	May be preferred by some women because it requires less frequent administration
Progestin Only			
Minipill	28 active pills	Varying doses	Reliable form of contraception but may not provide as much management of irregular cycles as COCPs
Subdermal Implant	Up to 3 years	Release rate of 60–70 mcg/day in the beginning and 25–30 mcg/day by the end of the 3 years	Some women may experience amenorrhea, while other women will not achieve regulation of their cycles
Injectable (DMPA)	Every 3 months	150 mg depot medroxyprogesterone acetate	Roughly half of women using this method will be amenorrheic after 3 months
Intrauterine Device	Up to 3 or 5 years depending on the device	Release rate of 20 mcg/day of levonorgestrel	Half of women will be amenorrheic after 12 months, and the rate increases the longer the device is in place

3.2 Combination Hormonal Contraception

As well as helping control menstrual irregularity, combination hormonal contraceptives can help to decrease the severity and frequency of vasomotor symptoms. Most women will see some level of relief with low-dose ethinyl estradiol formulations (20 mcg or less). Although this method can be helpful, some women may experience return of symptoms during the placebo pill week of their regimen. Skipping the placebo pills and continuing on to the next package of pills may be the best way to prevent this from happening. Pill regimens, risks, and benefits are described above in the menstrual irregularity section. Most women aged 40–49 who do not have other factors that increase their risk of adverse events with combination hormonal contraception can use this regimen safely. Providers may consider stopping the use of combination oral contraceptives around the age of 50–51, and if vasomotor symptoms persist, consider transitioning the patient to low-dose hormone replacement therapy.

3.3 Hormone Replacement Therapy

One of the most common and efficacious treatment options for vasomotor symptoms is hormone replacement therapy (HRT). Choosing HRT should be individualized to the patient's severity

of symptoms, and risks and benefits should be explored for each patient. Any contraindications to HRT that the patient might have must first be discussed. If there is any history of breast cancer, coronary heart disease, a previous venothrombotic event, or stroke, alternative therapies to HRT should be sought.

There are many different options for systemic estrogen dosing and administration. Dosing includes standard, low dose, and ultralow dose. Research has shown that many women experience relief of vasomotor symptoms with standard or low-dose estrogen, but treatment with ultralow dose has shown mixed results and is not currently FDA approved. The lowest effective dose for the shortest duration possible is recommended for all HRT (Practice Bulletin 141 2014).

Combination estrogen-progestin therapy is indicated for any woman who has not had a hysterectomy to prevent endometrial hyperplasia. Oral progestin is available in a combined formulation with estrogen or can be added individually to estrogen therapy, in which case it is suggested that they should be given at least 10–14 days every month. Some studies have found progestin therapy alone to be helpful in managing symptoms, but there is limited data on the long-term safety. One concern is that breast cancer is a risk with progestin-only therapy and it is not currently recommended as first line (Krause and Nakajima 2015).

3.4 Compounded Bioidentical Hormones

A treatment that is often promoted by supporters of herbal and dietary supplement-based health remedies is bioidentical hormones. These hormones are advertised as plant-derived hormones that have a molecular structure similar to hormones naturally produced by our bodies and there are claims that these hormones can be compounded to create an individualized preparation based off of a health-care provider's prescription. Oftentimes the hormones used for the compound preparations are not subjected to any formal testing so the exact safety, efficacy, purity, and potency of the hormones are unknown. There are also variables in the bioavailability and bioactivity of the various plant hormone sources used so that overdosing and underdosing of the preparations are a very real possibility. Furthermore, many of the individualized compounding formulas are based off of hormonal analysis from a salivary sample. There is no evidence that the levels of hormones in these types of samples are biologically representative. Overall, these compounded preparations that are not regulated by the FDA are not recommended for use (Committee opinion 532 2012).

3.5 Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

For women who have contraindications to hormonal therapy or who do not wish to use hormone-based treatment, there are other options for pharmacological management of their vasomotor symptoms. SSRIs and SNRIs are some of the most effective nonhormonal medications for treatment of vasomotor symptoms. Clinical response to these drugs for hot flashes is much faster than the time to response for depression:

- Paroxetine is the only FDA-approved SSRI for the treatment of hot flashes. It has been found to decrease both the severity and frequency of vasomotor symptoms. Paroxetine can be prescribed in doses of 7.5–25 mg daily. Common side effects include headache, dizziness, nausea, and insomnia, but these side effects will often decrease after around 12 weeks of use.
- In trials, escitalopram has shown promise for decreasing severity and frequency of symptoms at 10–20 mg daily. Common adverse effects include light-headedness, vivid dreams, nausea, and hyperhidrosis.
- Desvenlafaxine of the SNRI group has been found to result in a statistically significant decrease in symptoms.
- Sertraline and fluoxetine have often been found to provide little more symptom relief

than placebo and are not recommended as adequate treatment for vasomotor symptoms.

Current evidence suggests that SSRI or SNRI treatment may not be quite as effective as HRT, but these therapies remain a practical option for women who have contraindications or do not want to use hormone-based therapy (Drewe et al. 2015).

3.6 Gabapentin

Another nonhormonal option available for vasomotor symptom treatment is gabapentin. It has been shown to help decrease the severity and frequency of vasomotor symptoms similarly to therapy with SSRIs and SNRIs. However, the extent of relief seen with gabapentin treatment has also not been found to be as great as with HRT. Gabapentin can be prescribed in total doses from 600 mg to 1800 mg a day. Some of the most common side effects encountered with this treatment include dizziness, lethargy, headache, rash, and peripheral edema (Drewe et al. 2015).

3.7 Complementary Alternative Medicine

It is likely that providers will receive questions about the efficacy and safety of using natural or herbal supplements to help with vasomotor symptoms. Discussed below are some of the most common supplements used.

Actaea racemosa or *Cimicifuga racemosa*, otherwise known as black cohosh, is a member of the buttercup family and grows in North America. It is one of the most popular herbal supplements used by women experiencing perimenopausal and menopausal symptoms. There is mixed evidence; however some research has shown that there may be mild vasomotor symptom improvement over placebo in women taking black cohosh. Common side effects experienced when taking this supplement are GI distress, headaches, and rash. There have also been a small number of reports that this supplement has potentially been involved in causing hepatitis and hepatic failure, seizures, and cardiovascular disorders. The exact mechanism by which black cohosh decreases perimenopause symptoms is not yet known, and long-term effects have also not yet been studied. Due to the unknown mechanism of black cohosh, it has yet to be determined if this supplement has estrogenic activity as well as it is unclear what potential effects it might have on breast or genitourinary cancers. To date, there has not been any evidence that this supplement interacts with other medications, but proper research has so far not been conducted. Lastly, black cohosh is sold as a dietary supplement, and it is not regulated by the FDA meaning that the consistency of products sold may vary.

Phytoestrogens are plant-derived molecules that have similar activity in the body as human estrogen. One category of phytoestrogens is the isoflavones, and soy products contain two of the most estrogenic isoflavones that have been found. Different soy products contain varying amounts of isoflavones, and it has been recommended that women consume 40–80 mg of isoflavones per day if they want to use them as a treatment to combat vasomotor symptoms. There have been mixed results, but preliminary research has found that for some women, increasing the amount of soy-based products that they consume daily decreases the severity of their symptoms (Fugate and Church 2004). Research including standardized soy extract has also mixed results with some studies showing that it does help decrease the severity of symptoms and others suggesting that it is no more effective than the placebo. Along with inconsistent results, another problem with using soy products to decrease symptoms is that we lack knowledge of long-term effects (Table 2).

4 Vaginal Atrophy

Vaginal atrophy is often not a presenting symptom of perimenopause, but by late in the menopause transition, around one in five women may

Table 2 Vasomotor symptom management

Method	FDA Approved	Supporting Evidence	Additional Information
Combination Oral Contraception Pills	No	Yes	Some women may experience return of symptoms during placebo pill period
Hormone Replacement Therapy	Yes	Yes	One of the most effective forms of vasomotor symptom management
Bioidentical Hormones	No	No	Not recommended for symptom management
SSRIs/SNRIs			Affective nonhormonal option but symptom relief may not be as significant as with hormonal therapy
Paroxetine	Yes	Yes	
Escitalopram	No	Yes	
Desvenlafaxine	No	Yes	
Fluoxetine	No	No	Not recommended for adequate treatment of vasomotor symptoms
Sertraline	No	No	Not recommended for adequate treatment of vasomotor symptoms
Gabapentin	No	Yes	Affective nonhormonal option but symptom relief may not be as significant as with hormonal therapy
Complementary Alternative Medicine			
Black Cohosh	No	Mixed	Over-the-counter dietary supplement. Some women may experience mild relief of symptoms with this method
Phytoestrogens	No	Mixed	Results may vary based on the amount and type of phytoestrogens used

suffer from the symptoms of vaginal dryness. Vaginal dryness occurs because the epithelium of the vaginal will begin to atrophy due to decreasing estrogen levels, and this atrophy of the vaginal epithelium can lead to symptoms that affect a woman's sexual function. Many women have complaints of vaginal and vulvar dryness, dyspareunia, itching, and occasionally discharge.

4.1 Water-Based Lubricants and Vaginal Moisturizers

If the main symptom being encountered is dyspareunia, a nonhormonal option that can help is the use of water-based lubricants. Lubricants can be placed at the vaginal introitus before intercourse to help decrease friction and discomfort. Many over-the-counter options are available so that patients can find which brand works best for them.

Vaginal moisturizers are another nonhormonal, over-the-counter option to help with dyspareunia and other symptoms of vaginal atrophy. Moisturizers are used more regularly than lubricants, which, alternatively, are used primarily right before intercourse. Moisturizers may help with symptoms such as itching and feelings of dryness, as well as making intercourse more comfortable. The symptom relief that may be experienced with moisturizers is short term, and the moisturizer must be regularly administered to continue experiencing the benefits. Vaginal moisturizers do not result in long-term changes to the vaginal epithelium.

4.2 Vaginal Estrogen

For women solely experiencing vaginal atrophy and its related symptoms, local estrogen is an effective therapy. Local estrogens can be delivered by cream, tablet, or ring formulations. All

forms use a low dose of estrogen, and the form of administration can be tailored to patient preference. The cream often is applied daily for 1–2 weeks and then can be used as needed for as long as the therapy is desired. Many women find the ring to be a practical choice because it can be used for 3 months at a time. There is some evidence of systemic absorption with the use of local estrogen, and there has been concern that this absorption could lead to an increased risk of endometrial hyperplasia. So far, no research has found that the systemically absorbed estrogen has increased occurrence of endometrial hyperplasia when compared to a placebo. At this time, the use of progestin with local estrogen therapy is not required (Practice Bulletin 141).

5 Urinary Incontinence

As women age, many will begin to experience urinary incontinence with stress incontinence being the most common subtype encountered. There is mixed evidence on whether increasing urinary incontinence is caused by hormonal changes experienced during perimenopause or if it is just general aging that worsens incontinence. Some basic symptom management will be discussed but providers should understand that if the initial management strategies suggested do not provide adequate relief, it may be best to refer the patient to a urologist or urogynecologist for further evaluation and/or treatment.

5.1 Lifestyle Modifications and Behavioral Therapy

Just like with many of the other perimenopausal symptoms, the first step to managing urinary incontinence is lifestyle modification. Losing weight and smoking cessation can have significant positive impacts on controlling incontinence. Women also need to ensure that they are getting adequate, but not excessive, hydration and should be encouraged to decrease consumption of caffeinated and alcoholic beverages.

Behavioral therapy strategies are another important method that can be used as first-line therapy for stress incontinence. Bladder training involves frequent voluntary urination and helps to keep the volume level of the bladder low while training the central nervous system to decrease urgency. Initially, it is recommended that women voluntarily void every two hours. If a feeling of urgency is experienced in between voids, women should use relaxation techniques to control the feeling. Women should stand still or sit down while concentrating on breathing and contracting their pelvic muscles to help decrease the feeling of urgency. Once the feeling has passed, women should slowly walk to the restroom to void. When women can go 2 days without experiencing any leakage, they can increase the time between voluntary voids by 30 min to an hour. Bladder training can take several weeks to be successful so women should be made aware of this time commitment and encouraged to maintain training even if they do not perceive immediate results.

Along with bladder training, strengthening the pelvic muscles can also help decrease incontinence. Pelvic muscle exercises also known as Kegel exercises involve strengthening the muscular urethra closure mechanism. The muscles being used are the ones that are used to stop a stream of urine when urinating. Women should understand how to do the exercises properly and can start by doing three to four sets of ten repetitions daily. It is important to make sure women understand that they should not make a habit of doing this exercise while urinating, however, as it can adversely lead to a decrease in continence. Just as with the bladder training, pelvic floor strengthening can take several weeks for women to notice improvement, and the best results can be seen when both bladder training and Kegel exercises are used together.

5.2 Estrogen

Local estrogen has been shown to slightly improve stress incontinence symptoms. Currently, local estrogen therapy is only used in

women that have concurrent symptoms of vaginal atrophy. Systemic estrogen with HRT has been shown to worsen symptoms of stress incontinence.

6 Mood Changes

In general, illnesses such as major depressive disorder and generalized anxiety disorder are seen more frequently in women than their male counterparts. During the time when women are experiencing perimenopause, it is possible that there are other events taking place in women's lives that may contribute to increased stress or discouraging feelings. Many women might experience other health and physical changes around this time, and many could be going through social transitions as well. All of these things, together with fluctuating hormone levels, might increase some women's chances of experiencing mental health disorders. Patients should be screened for these disorders if they are experiencing mood change symptoms, and the appropriate treatment should be implemented if they meet criteria. For women who are having mild mood changes, the suggestions below may help.

6.1 Lifestyle Modifications

An important first step toward improving mood changes in perimenopause is making sure the patient's lifestyle and daily habits provide them with good overall health. Eating a balanced diet and daily physical activity are vital places to start. Patients should be encouraged to watch their calorie and nutrient intake, drink adequate amounts of water, and aim to get 30 min of exercise a day, 5 days a week. Other things like making sure the patient isn't drinking excessive amounts of caffeine or alcohol are also important. As mentioned previously, exercise has not been found to absolutely eliminate perimenopause symptoms, but some patients find that regular exercise helps them to feel overall healthier.

6.2 Pharmacotherapy

Some women may experience improvement in mood swings when taking combination hormonal contraception or low-dose SSRIs. The different types, benefits, and risks are discussed earlier in the chapter and applied here as well.

7 Conclusion

Finding the best treatment for a patient's perimenopause symptoms depends on many patient factors. First, the severity and frequency of symptoms should be considered. The appropriate level of treatment should be initiated to match the intensity of the patient's symptoms. Some women may be able to start with lifestyle modifications, behavioral therapies, and any approved over-the-counter therapies before moving on to prescribed treatments if they have only mild symptoms. The patient's past medical history can also help guide treatment selection. It is imperative to making sure that the patient has no contraindications to a selected treatment as well as no previous health conditions that might increase the likelihood of adverse effects from the chosen therapy. Another important goal is to be able to relieve as many symptoms as possible with the fewest treatment methods. Several of the treatments described in this chapter can be used to combat multiple perimenopausal symptoms, and it is just a manner of discussing with the patient their particular set of symptoms and finding a therapy that can cover as many of those symptoms as possible. Overall, communication with the patient and being familiar with the common symptoms of perimenopause and how best to treat them will help guide physicians to the appropriate management plan.

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Management of Menopausal Symptoms

Cassandra M. Roeca and Elizabeth S. Ginsburg

Contents

Abstract

Menopause is the point at which oocytes are depleted and there is a marked drop in circulating estrogen and progesterone levels. Common symptoms associated with menopause and discussed in this review include vasomotor spasms, vulvovaginal atrophy, diminished bone strength, decreased libido, and neuropsychological changes. The biological etiologies of these symptoms stem from a deprivation of estrogen in the body. The core of menopausal symptom treatment has traditionally been hormone replacement to restore the underlying estrogen deficiency. In most cases, estrogen therapy is the most effective treatment of menopausal symptoms. However, hormone replacement, particularly systemic therapy, should be utilized with caution as it can increase risk of venous thromboembolic disease, breast cancer, and stroke. There are now alternative, non-hormonal options available to women who are unable to utilize hormone replacement or who do not want to assume its risks. Understanding the risks of both hormonal and non-hormonal treatment modalities is crucial for the provider who works with women who are transitioning into menopause or who are postmenopausal. This review will describe available treatments for commonly experienced symptoms of menopause.

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1 Introduction

Menopause is defined as beginning 1 year after a woman's last menstrual period and marks confirmed cessation of ovarian function. The menopausal transition initiates roughly 4 years prior to menopause, with the median age of menopause in the United States being 51 years. In the early transitional years, women typically experience an increase in cycle length accompanied by cycle irregularity, including anovulation or hypermenorrhea or both. During the late menopause transition, women may miss at least three periods a year and experience anovulation for two or more months. Estrogen levels remain normal, if not slightly elevated, until 1 year prior to menopause. Unopposed estrogen exposure during the menopausal transition due to anovulation, estrogen excess, or exogenous estrogen administration may increase risk for endometrial hyperplasia and atypia. Women presenting with abnormal uterine bleeding within this population should be ruled out for underlying malignancy with endometrial biopsy. While this population is at risk for developing endometrial hyperplasia, only 1–2 % of perimenopausal women presenting with abnormal uterine bleeding symptoms will have endometrial cancer (Feldman et al. 1994). Follicular depletion prior to menopause decreases inhibin production, leading to a subsequent rise in follicular stimulating hormone (FSH). Lutenizing hormone (LH) levels remain normal until the time of menopause, after which LH levels rise. A reduction in mature follicle formation results in declining progesterone levels. Testosterone levels may remain unchanged or decrease slightly in early postmenopausal women, but by late menopause, there is a notable decline in serum testosterone. Sex hormone-binding globulin (SHBG) levels decrease in menopause which leads to decreased total body levels but increased levels of unbound estrogen and testosterone. These hormonal changes may result in many symptoms that accompany menopause, the treatments of which will be discussed below.

2 Vasomotor Symptoms

Thermoregulatory changes, commonly referred to as "hot flushes," affect over half of pre- or postmenopausal women, making them the most common symptom experienced. Most women who experience vasomotor symptoms will be symptomatic for 1–2 years, but for some, symptoms can persist for many years after menopause. A typical hot flush begins as a flushing sensation that starts on the upper body and spreads to the neck and face, lasting for 1–5 min. During a hot flush, body temperature initially increases by up to 7 °C, causing a responsive capillary dilation. This leads to diaphoresis, palpitations, and subsequent cooling. Disruption of the thermoregulatory zone of the hypothalamus due to decreasing estrogen levels and possibly altered neurotransmitters are thought to lead to altered thermal regulation, and thus, the development of hot flushes. Estrogen may regulate inhibitory presynaptic adrenergic receptors, and a decrease in estrogen, or estrogen withdrawal, has been proposed to contribute to increased norepinephrine release which stimulates a corporal heat-loss response (Rapkin 2007). Declining estrogen levels have been found to decrease serotonin levels, leading to a compensatory increase in postsynaptic serotonin receptors, possibly increasing the sensitivity to serotonin which triggers a heat-loss response (Slopien et al. 2003). Other factors that may be associated with development of thermoregulatory changes include: low socioeconomic status, high BMI, smoking, lack of exercise, and history of depression.

2.1 Hormonal Therapies

Systemic hormone replacement therapy (HRT) with estrogen is the most effective treatment of

Table 1 Therapies for vasomotor symptoms

	Brand name(s)	Dosing
Estrogen formulations		
Oral CEE	Premarin	0.3–0.625 mg/d
Oral 17β-estradiol	Estrace	0.5–1 mg/d
Oral synthetic estrogen	Enjuvia	0.3–0.625 mg/d
17β-estradiol transdermal patch	Alora, Climara, Estraderm, Menostar, Vivelle-dot	0.025–0.05 mg/d 1–2x/wk
17β-estradiol transdermal gel	EstroGel, Estrasorb, Divigel, Elestrin	0.25–1 mg/d
17β-estradiol transdermal spray	Evamist	1.53 mg/d
Combined formulations		
Oral cyclic CEE + MPA	Premphase	0.625 mg/d CEE × 14d then 0.625 mg/d CEE/5.0 mg/d MPA × 14d
Oral continuous CEE + MPA	Prempro	0.3–0.625 mg/d CEE and 1.5–5 mg/d MPA
Oral continuous 17β-estradiol + progestin[a]	Activella, Angeliq	0.5–1 mg/d E + 0.1–0.5 mg/d P
17β-estradiol + progestin[a] transdermal patch	CombiPatch, Climara Pro	0.05 mg E + 0.14 mg P 2x/wk 0.045 mg E + 0.014 mg P 1x/wk
Oral CE + bazedoxifene	Duavee	0.45 mg/day + 20 mg/day
Non-hormonal formulations		
Paroxetine	Paxil	7.5 mg/day

CEE conjugated equine estrogen, *mg/d* milligrams per day, *x/wk* times per week, *MPA* medroxyprogesterone acetate, *E* 17β-estradiol, *P* progestin, *CE* conjugated estrogen

[a]Activella – progestin is norethindrone acetate, Angeliq – progestin is drospirenone, CombiPatch – progestin is norethindrone acetate, Climara Pro – progestin is levonorgestrel

bothersome vasomotor symptoms. The Women's Health Initiative demonstrated improvement of vasomotor symptoms in 85 % of women taking estrogen plus progesterone (Barnabei et al. 2005). Estrogen therapy is therefore the gold standard for bothersome hot flushes. Estrogen preparations are available in conjugated, bioidentical, and transdermal forms with or without progesterone. Bioidentical formulations are chemical preparations (i.e., 17β-estradiol) that mimic the action of the endogenous hormone. Hormonal treatment should only be initiated for bothersome vasomotor symptoms and should not be initiated for primary prevention of menopause symptoms or cardiovascular disease. The use of estrogen therapy is not without its risks. In the Women's Health Initiative (WHI) study in 2002, the use of equine estrogen therapy alone increased the risks of coronary heart disease events, pulmonary embolism, and stroke (Rossouw et al. 2002). Studies have since sought to prove that modern estradiol formulations and starting HRT in early menopause prior to development of atherosclerotic disease decreases overall CVD risk, but a definitive protective effect has not yet been demonstrated. Approved estrogen formulations for the treatment of vasomotor symptoms are listed in Table 1. Bazedoxefine is a selective estrogen receptor modulator (SERM) combined with conjugated estrogen (CE) approved by the FDA to treat vasomotor symptoms in women with an intact uterus. This combination of SERM and CE is termed tissue-selective estrogen complex (TSEC,) and is designed to provide better treatment than either drug independently. BZA has agonist properties that promote bone growth and diminish hot flushes and antagonistic properties that inhibit uterine and breast tissue proliferation. The SMART-1 trial studied the effects of BZA/CE on vasomotor symptoms and demonstrated a 51–87 % decrease in daily hot flush symptoms compared to a 0–17 % decrease in the placebo arm (Lobo et al. 2009). BZA/CE demonstrated a similar adverse event profile when compared with

placebo. Progesterone therapy alone is not recommended for treatment of bothersome vasomotor symptoms, though it may improve vasomotor symptoms both with estrogen and alone. The duration of recommended use of estrogen therapies is not concrete, and discontinuation of HRT results in return of vasomotor symptoms in up to half of women. Whereas patients were previously counseled not to continue treatment past age 65, the American College of Obstetricians and Gynecologists (ACOG) recommends that treatment duration be determined on a case-by-case basis, with the goal of treating for the shortest duration possible while taking into account a woman's clinical picture and risk benefit of continuing hormone replacement therapy. Estrogen therapy is contraindicated in women with a history of breast cancer, liver disease, abnormal uterine or vaginal bleeding, estrogen-dependent cancer, history of deep venous thromboembolism or pulmonary embolism, and pregnancy.

2.2 Non-hormonal Therapies

The only non-hormonal FDA-approved medication for the treatment of vasomotor symptoms is paroxetine mesylate. Paroxetine reduces hot flushes in women without depression by nearly 30 % (Simon et al. 2013). Selective serotonin reuptake inhibitors (SSRIs) generally improve symptoms after 8 weeks of treatment. While SSRIs are inferior to HRT for reducing vasomotor symptoms, these medications are a reliable alternative for women in whom hormonal therapy is contraindicated. Risk factors with SSRIs include a black box warning for possible suicidal ideation, along with other common side effects including dry mouth, dizziness, and sexual dysfunction. Other non-hormonal therapies, including serotonin-norepinephrine reuptake inhibitors (SNRIs,) Clonidine, and Gabapentin, have demonstrated therapeutic benefit for vasomotor symptoms. Desvenlafaxine, an SNRI, decreased the number of hot flushes by 62 % compared to 38 % in the placebo arm of a randomized controlled trial and maintained a treatment effect for a year (Pinkerton et al. 2013). Trials evaluating Clonidine have demonstrated a modest reduction of hot flush frequency ranging from 24 % to 44 % (Nelson et al. 2006). Women receiving Gabapentin dosed 900 mg/day experienced a decreased number of vasomotor symptoms by roughly 45 % in two trials (Guttuso et al. 2003). These therapies, however, have not demonstrated superiority to estrogen therapies and currently are not approved by the FDA for treatment. Vitamin E has demonstrated a very mild benefit in decreasing hot flushes by one event per day (Barton et al. 1998). Phytoestrogens, a group of plant-derived estrogen-like supplements found in soy and red clover, have not been demonstrated to effectively reduce hot flushes, and many studies performed have demonstrated a large placebo effect. The potential benefits of acupuncture have thus far not demonstrated significant reduction of hot flushes compared to placebo in a randomized controlled trial. Herbal treatments of menopause include Chinese medicines dong quai and dang gui bu xue tang, black cohosh, St. John's wort, and ginkgo biloba. There is proposed benefit of combining traditional Chinese medicine with acupuncture in treating vasomotor symptoms, and there are preliminary trials working to demonstrate that these modalities are as effective as hormone therapy for decreasing hot flushes. However, some trials have suggested no benefit, and there is not enough data demonstrating efficacy and safety to support the routine use of these therapies. There are no studies definitively demonstrating that exercise confers benefit to decrease vasomotor symptoms in menopause, however it may improve quality of life and mood. Other changes women can make to their daily lives to possibly improve symptoms include dressing in layers, drinking cold beverages, keeping a cooler living temperature, and avoiding possible triggers like alcohol and caffeine.

3 Vaginal Atrophy

Atrophy of the vulva and vagina in women occurs due to decreased estrogen receptor stimulation accompanied by menopause. Architectural changes of the urogenital tract include loss of

Table 2 Local therapies for vaginal atrophy

	Brand name	Dosing
Estrogen formulations		
17β-estradiol ring	Estring	2 mg for 3 months
Estradiol tablet	Vagifem	10–25 μg, 1 tab/d of 2wk, then 1 tab 2/wk
17β-estradiol cream	Estrace Cream	2 g/d
CEE cream	Premarin Cream	0.5–2 g/d
SERM		
Ospemifene	Osphena	60 mg/d

mg milligrams, *μg* micrograms, *d* day, *wk* week, *g* grams, *CEE* conjugated equine estrogen, *SERM* selective estrogen-receptor modulator

vaginal surface epithelium with a decrease in superficial cells and increased parabasal cells, decreased vaginal wall blood flow and thus decreased vaginal connective tissue hydration, soft tissue atrophy of the vulva, and eventually, vestibular narrowing. There is also a decrease in sebaceous gland secretions and an increase in vaginal pH. These changes lead to common symptoms including vulvar and vaginal itching and dyspareunia and place women at higher risk of vaginal irritation and urinary tract infections (Levine et al. 2008).

Hormonal therapies: Estrogen therapy, both systemic and local, decreases vaginal atrophy and dryness. Low-dose systemic estrogen is approved for treatment of vaginal atrophy; however, for women in whom vaginal dryness is the only complaint, local therapy is recommended (see Table 2). FDA-approved vaginal estrogen therapies include an estradiol ring, estradiol vaginal tablet, estradiol cream, or conjugated estrogen cream (Table 2). Vaginal creams or tablets are used daily for 1–2 weeks and then once or twice a week thereafter, while rings are replaced once every 3 months. Overall, the estrogen therapy in ring form may provide the most patient satisfaction compared to creams and tablets, while tablets may be preferred to creams. There is possible risk of increased endometrial cancer risk due to systemic absorption of estrogen, but the current data does not support a need for additional surveillance of endometrial cancer for women utilizing vaginal estrogens. However, due to the concern of possible systemic absorption, women with a history of breast cancer are not recommended to utilize vaginal estrogens as first-line therapy and should only try short-term vaginal estrogen treatment for refractory symptoms and after consultation with her oncologist.

Non-hormonal therapies: SERMs have demonstrated efficacy in the treatment of bothersome vaginal dryness by acting as agonists on the vaginal mucosa and increasing the number of superficial and intermediate cells. In the SMART-1 study, patients treated with BZA/CE reported improved dyspareunia (Lobo et al. 2009). However, the only SERM approved by the FDA for treatment of symptomatic vaginal atrophy is ospemifene. Studies have compared ospemifene with placebo and demonstrated improvement of vaginal atrophy with 30 and 60 mg daily compared with placebo and a reduction in dyspareunia with 60 mg/day (Bachmann and Komi 2010). The most common side effects noted with ospemifene are vasomotor symptoms, and though not common, there is a possible risk of endometrial proliferation. Lubricants and moisturizers come in water-based or silicone-based preparations and may alleviate vaginal dryness symptoms, though they are not approved by the FDA for this purpose. Lubricants can be applied to the vulva, vagina, or partner's penis tip prior to intercourse to decrease friction and irritation. Moisturizers do not need to be applied prior to intercourse, though they can help to alleviate painful sex. Moisturizers can be applied from three times weekly to daily, sometimes with an applicator, and retain lubrication of the vaginal mucosa. Vaginal moisturizers are utilized to reduce itching, irritation, and dyspareunia. The combination of a moisturizer with pre-intercourse application of lubricant may be beneficial for some women. Moisturizers are

Table 3 Therapies for osteoporosis

	Brand Name(s)	Dosing
Bisphosphonates		
Oral Alendronate	Fosamax, Fosamax Plus D[a]	Preventative: 5 mg/d or 35 mg/wk Treatment: 10 mg/d or 70 mg/wk (pill or solution)
Oral Risedronate	Actonel, Atelvia	Preventative: 5 mg/d, 35 mg/wk Treatment: 35 mg/wk DR, 75 mg/mo on two consecutive days, 150 mg/mo
Oral Ibandronate	Boniva	150 mg/mo
IV Ibandronate	Boniva IV	3 mg every 3 months
IV Zoledronic Acid	Reclast	Preventative: 5 mg x1 Treatment: 5 mg/y
Hormonal formulations		
Systemic estrogens alone or with progestin	See Table 1	
CE + bazedoxifene	See Table 1	
SERM		
Raloxifene	Evista	60 mg/d
Monoclonal antibody		
SC Denosumab	Prolia	60 mg every 6 months
Recombinant hPTH		
Teripartide	Forteo	20 μg/d
Calcitonin		
Intranasal calcitonin	Fortical	200 IU/d
SC or IM calcitonin	Miacalcin	100 IU every other day

mg/d milligrams per day, *mg/wk* milligrams per week, *mg/mo* milligrams per month, *μ/d* micrograms per day, *SC* subcutaneous, *hPTH* human parathyroid hormone, *IM* intramuscular
[a]Contains vitamin D3 2,800 IU/wk

sold over the counter, so cost can be prohibitive for some patients. Dietary and compounded phytoestrogens, black cohosh, and herbal remedies have not demonstrated significant benefit in improving vaginal atrophy.

4 Bone Strength

Bone resorption increases with the decreasing estrogen levels that accompany the transition to menopause and leads to decreased bone mass which in turn can lead to osteoporosis and increased fracture risk. Estrogen, calcium, and vitamin D play pivotal roles in maintaining bone health. Estrogen inhibits osteoblast production of RANKL, a ligand that binds RANK receptors on osteoclasts to stimulate activation and bone resorption. Estrogen also increases osteoblast production of osteoprotegerin (OPG) which inhibits RANKL. Thus, decreasing estrogen levels promote osteoclast resorption of bone. Adequate intake of calcium inhibits parathyroid hormone (PTH) breakdown of bone. However, aging leads to a decrease in calcium intestinal absorption and subsequently rising PTH hormone activates osteoclast activity to increase serum calcium and promote vitamin D production. Decreased estrogen also increases bone sensitivity to PTH. Vitamin D increases intestinal absorption of calcium and promotes renal calcium reabsorption. Thus, adequate vitamin D and calcium intake promote healthy bone mass density. Bone mass typically declines 2–5 % per year during the first 10 years after menopause and then 1 % yearly thereafter. The United States Preventative Services Task Force (USPSTF) and ACOG both recommend bone mineral density screening via dual x-ray absorptiometry (DEXA) scan in women >65 years or post/perimenopausal women with risk factors for osteoporosis. Risk factors for

osteoporosis include early menopause (<45 years), corticosteroid use (>3 months), prior fragility fracture, high fall risk, family history of osteoporotic fracture, and primary hyperparathyroidism. White race confers a higher risk of osteoporosis. The DEXA scan result of importance is the T score which is the standard deviation from the peak BMD of an average, healthy, white female. The fracture risk assessment tool (FRAX) is another tool available to screen women for osteoporotic fracture risk. Medical therapy for osteoporosis is recommended for postmenopausal women who have had a vertebral or hip fracture, with a DEXA T score less than −2.5 or who have a T score from −1.0 to −2.5 and a 10-year FRAX major fracture risk of at least 20 % or 3 % hip fracture risk.

Hormonal therapies: Systemic estrogen replacement with or without progesterone promotes bone formation, decreases fractures, and is currently approved for the prevention of osteoporosis. Initiation of hormonal therapy for prevention of osteoporosis should be reserved for patients who experience other menopause symptoms such as vaginal atrophy or hot flushes, though therapeutic benefit and risk can be compared with other pharmaceutical options. Estrogen therapy, with or without progesterone, is available in oral or patch forms and is approved for the prevention of osteoporosis (see Table 3). The Postmenopausal Estrogen/Progestin Interventions trial (PEPI) and the WHI study both demonstrated significantly increased spine and hip BMD with HRT (Cauley et al. 2003; Greendale et al. 1996). Combined estrogen/progestin formulations confer over a 25 % reduction in fracture risk. CE formulations are available in oral forms between 0.3 and 1.25 mg/day and 17B-estradiol in patch forms between 0.025 and 0.14 mg/day. Combinations with progesterone include oral continuous cyclic or continuous combined (see Table 1). The North American Menopause Society (NAMS) recommends utilizing the lowest effective dose for the desired treatment result. While there is no clearly delineated time when estrogen therapy should be initiated, commencing treatment earlier in menopause is encouraged.

The TSEC CE/bazedoxifene is approved for prevention of osteoporosis and simultaneously treats vasomotor symptoms (0.045 CE + 20 mg). After discontinuation of estrogen therapy, bone mineral density begins to decrease within the first 1–2 years, often to levels similar to that of untreated patients by 5 years after discontinuation, and women may need to be placed on an alternate treatment method (Karim et al. 2011).

Non-hormonal therapies: Bisphosphonates inhibit bone resorption by osteoclasts, decrease fracture risk, and were the first medications approved for both treatment and prevention of osteoporosis. Therapy with bisphosphonates in women with osteoporosis has demonstrated a 40–70 % reduction in vertebral fracture risk and roughly 50 % hip fracture risk reduction (McClung 2003). Bisphosphonates are the first-line therapy for treatment of osteoporosis in postmenopausal women. Alendronate, Risedronate, Ibandronate, and Zoledronic acid are bisphosphonates approved by the FDA. Alendronate is available in oral solution or pill form in both treatment and preventative doses. Bisphosphonates have a favorable safety profile, with the main side effect being GI upset, but also possible osteonecrosis of the jaw. Discontinuation of bisphosphonates after therapy of at least 5 years has a continued effect on BMD for an additional 5 years. Therapy duration with bisphosphonates is indeterminate.

The SERM, Raloxifene, is approved for treatment and prevention of osteoporosis. In the MORE trial, 60 mg a day decreased vertebral fracture risk by 39 % over 4 years (Delmas et al. 2002). Raloxifene may also confer a reduction in breast cancer risk. Raloxifene is best suited for younger females as it may increase venous clot and stroke risk.

Denosumab, a monoclonal antibody against RANK-L that inhibits osteoclast activation and proliferation, is approved for the treatment of osteoporosis. The FREEDOM trial demonstrated that 60 mg of subcutaneous Denosumab administered once every 6 months significantly decreased hip and non-vertebral fracture risk by 40 % and 20 %, respectively (Cummings et al. 2009).

Common adverse reactions include eczema and cellulitis at the site of injection.

Recombinant human parathyroid hormone 1–34, teriparatide, is approved for the treatment of women at high risk of osteoporosis. Teriparatide promotes bone growth via anabolic effects by recruiting osteoblasts and decreasing osteoblast death. This therapy demonstrated over a 60 % decrease in vertebral and non-vertebral fracture risk (Neer 2001). Therapy duration, however, is limited to 2 years as there is risk of bone malignancy and osteosarcoma, and alternate therapy is typically swiftly indicated as BMD quickly decreases after cessation of teriparatide.

Calcitonin inhibits calcium reabsorption from bone by osteoclasts and decreases risk of vertebral fractures. It is a protein, and thus at risk of degradation in the stomach, so pharmaceutically it is available in nasal, intramuscular, or subcutaneous preparations. This therapy is indicated for the treatment of osteoporosis in women greater than 5 years from their last menstrual period. Calcitonin is not considered a first-line drug by the NAMS as it is less efficacious than alternative therapies. Calcitonin is derived from salmon, and available dosed 200 IU/day intranasally, or 100 units SC or IM every other day. It also has an analgesic effect with osteoporotic fractures. Typical side effects include local site reactions.

Calcium, vitamin D, exercise, and a balanced diet are recommended for prevention of osteoporosis in postmenopausal women. The WHI demonstrated that women who reliably took daily calcium 1000 mg and 400 IU vitamin D had a significantly reduced risk of hip fracture (Jackson et al. 2006). Calcium supplementation, however, may increase risk of cardiovascular disease by depositing in vessels and increasing plaque thickness and is associated with other side effects including gastrointestinal upset and kidney stones. Studies evaluating the risk of MI, stroke, and sudden death with calcium supplementation are ongoing. Currently, per the Institute of Medicine (IOM), the recommended calcium intake is 1200 mg/day and for vitamin D is 600 IU/day. The IOM also recommends that postmenopausal women consume 46 g of protein daily to promote healthy bone density. Regular exercise may improve BMD, not simply due to weight-bearing on specific bone areas but also due to improvement in balance, flexibility, and muscle tone.

5 Libido

Women continue to be sexually active throughout their lifetime; however, declining female sexual activity is associated with increasing age. Important determinants of sexual well-being in the elderly include availability of a satisfactory partner and adequate physical health. Divorce and partner death also greatly impact libido in postmenopausal women. A major contributor to sexual dysfunction in postmenopausal women is vulvovaginal atrophy, affecting over 50 % of postmenopausal women who complain of impaired sexual function (Levine et al. 2008). Decreased estradiol does not appear to contribute to declining sexual function but is related to pain with intercourse. Other risk factors for dyspareunia include chronic pelvic pain, pelvic organ prolapse, arthritis, fibromyalgia, and prior gynecologic surgery as it can shorten the vagina. A number of social factors contribute to decreased libido in postmenopausal women, including increased stress, smoking, and alcohol. Reduced androgen levels in postmenopausal women also contribute to decreased libido and sexual function.

Hormonal therapies: Both estrogen and testosterone replacement may improve sexual function and mood in postmenopausal women. Estrogen is superior to progesterone for improving mood and overall sexual satisfaction and improves dyspareunia related to vaginal atrophy (Dennerstein et al. 2002). The addition of testosterone replacement in women already utilizing estrogen replacement improves overall sexual satisfaction, both in women who have undergone natural or surgical menopause, who have low to low-normal serum testosterone. Testosterone levels are elevated to normal or even high-normal levels when coadministered with estradiol, likely due to increased levels of sex hormone-binding globulin, which decreases testosterone clearance and increases total body testosterone levels. Transdermal testosterone-dosed 300 mcg/day

with estrogen replacement has benefits on sexual satisfaction in women who have undergone surgical menopause by increasing the rates of sexual desire, fantasies, and intercourse (Shifren et al. 2000). Testosterone therapy alone was studied in the APHRODITE study, a double-blind placebo-controlled trial, and testosterone therapy increased enjoyable sexual experiences by 13 % compared to placebo (Davis et al. 2008). However, testosterone replacement therapy is not FDA-approved for routine postmenopausal use due to a lack of long-term safety profile. Risks of androgen therapy include unfavorable lipid profile, hirsutism, and acne, though there has not been a significantly demonstrable increase in these adverse outcomes when testosterone was administered with estrogen hormonal therapy. There is a possible risk of breast cancer with androgen supplementation as observed in the APHRODITE study; however, studies remain mixed as to whether testosterone in fact suppresses or promotes breast cell proliferation.

Non-hormonal therapies: For patients who are in a relationship, couple's counseling may elevate libido and sexual drive by identifying possible underlying physical or psychological barriers to fulfilling sexual encounters. Lifestyle changes including healthy diet modifications, reduced alcohol intake, cessation of smoking, and relaxation exercises may improve sexual functioning as well.

6 Neuropsychological Changes

Social, cultural, and hormonal factors have been associated with mood and cognitive changes that accompany the menopause transition. Women who have higher estrogen level spikes during the transition to menopause may be at higher risk of depression. There are many changes that accompany menopause, one being that women can no longer conceive, which in itself may trigger mental anxiety and depression. A longitudinal analysis of the Massachusetts Women's Health Study suggests that a history of depression is the most common risk factor for future depression. They also demonstrated that a lengthier transition to menopause (27 months or greater) was associated with depression but likely due to an increase in menopausal symptoms (Avis et al. 2001). Older premenopausal women are more likely to become depressed if they are nulliparous, smokers, or are no longer with a prior spouse. Different cultures harbor their unique attitudes toward menopause, which may influence how women feel as physiologic changes take effect. Cognitive changes such as impaired function and memory are associated with age but may also be due to hormonal changes. Impaired sleep function may also accompany menopause and result in poor cognition, irritability, and depressed symptoms. Sleep difficulties related to menopause are often to due hot vasomotor symptoms but can also be related to age-related physical changes such as pharyngeal narrowing, lighter sleeping, chronic health conditions, and restless sleep partners.

6.1 Hormonal Therapies

Some studies suggest that treatment of vasomotor symptoms alleviates disruption of sleep and elevates mood, thus making systemic estrogen therapies and TSECs possible therapies to improve quality of life in postmenopausal women. While some women may present with disruption of sleep or depression and presenting symptoms, underlying vasomotor symptoms may be the culprit and treatment with therapies as described above may subsequently resolve sleep and psychologic disturbances.

6.2 Non-hormonal Therapies

Sleep aids may help improve insomnia and quality of life. Sleep aids, aside from improving sleep in peri- and early postmenopausal women, can enhance mood, menopause-related symptoms, and quality of life.

Antidepressant medications, along with therapy and counseling, may improve symptoms of depression in postmenopausal females. Women not on estrogen replacement therapy who suffer

from depression can benefit from SSRIs or SNRIs for treatment.

7 Conclusion

Menopause is a period marked by estrogen depletion that can lead to deleterious side effects that affect women physically and emotionally. There are many different therapies, both hormonal and non-hormonal, available to treat symptoms of menopause. Choosing the appropriate therapy for a patient should be based on the patient's individual symptoms, medical history, and goals of care. As a general rule for treating vasomotor spasms and vulvovaginal complaints, the most common bothersome symptoms of menopause, the lowest dose of therapy for the shortest amount of time necessary, should be used. While estrogen and progesterone therapies benefit bone health, the first line for both treatment and prevention of osteoporosis in postmenopausal women is bisphosphonate therapy, which is available in many forms to accommodate ease and frequency of therapy administration. Women should be asked about symptoms related to menopause by their providers at each visit to evaluate the need for management initiation, duration, and cessation.

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Diagnosis and Management of Postmenopausal Bleeding

Trevin C. Lau and Lisa B. Spiryda

Contents

Abstract

Postmenopausal bleeding refers to any uterine bleeding that occurs after a woman reaches menopause and accounts for up to 5 % of gynecological office visits. Excluding an endometrial malignancy is the key component to the work-up. Ultimately, the management of these patients is dictated by the diagnosis. The differential diagnosis ranges from gynecologic causes to non-gynecologic causes, including urologic and gastrointestinal etiologies.

Keywords

Postmenopausal bleeding • Endometrial hyperplasia • Endometrial cancer • Endometrial polyp • Urogenital atrophy • Endometrial biopsy • Transvaginal ultrasound • Endometrial thickness

1 Introduction

Postmenopausal bleeding is a common gynecological complaint occurring in 5–10 % of postmenopausal women. The differential diagnosis includes urogenital atrophy, genital tract lesions, endometrial polyps, endometrial hyperplasia or malignancy, medications, as well as non-gynecologic sources of bleeding (Table 1). Evaluation should focus on excluding uterine malignancy, which accounts for about 10 % of postmenopausal bleeding cases and may be lethal

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Table 1 Differential diagnosis of postmenopausal bleeding

Gynecologic	Endometrial polyp Urogenital atrophy Endometrial hyperplasia Uterine cancer Endometritis Uterine fibroid Endocervical polyp Cervicitis Cervical cancer Estrogen-secreting ovarian cancer
Urologic	Urinary tract infection Urethral caruncle/polyp Urologic cancer
Gastrointestinal	Hemorrhoids Diverticulitis Inflammatory bowel disease Gastrointestinal cancer
Medications	Hormone therapy Anticoagulation therapy
Others	Trauma Foreign body

if not identified and treated at an early stage. Management depends on the underlying cause. This chapter offers guidance on the diagnostic evaluation and management of postmenopausal bleeding.

2 Presentation

Postmenopausal bleeding (PMB) refers to bleeding from the genital tract in a menopausal woman. Patients present with "vaginal" bleeding that varies in quantity, quality, and duration. Patients may complain of one episode of brownish spotting, recurrent red staining, or several days of heavy bleeding resembling a menses. Bleeding may arise from the vulva, vagina, cervix, endometrium of the uterus, and fallopian tubes. Bleeding from the urinary tract or gastrointestinal tract may be confused for vaginal bleeding, and a detailed history and physical exam are necessary to discern the source of bleeding. PMB may also be occult in women with cervical stenosis; these patients may present with pelvic pain and are found to have hematometra on imaging.

3 Epidemiology

About 10 % of women experience PMB and the chance of occurrence is highest within the first year after menopause (Astrup and Olivarius 2004). This complaint accounts for 5 % of gynecology visits. The overall incidence of endometrial cancer in women with PMB is approximately 5–10 % (Moodley and Roberts 2004; Burbos et al. 2010, 2012) and can be as high as 25 % in patients with pertinent risk factors and increasing age.

3.1 Risk Factors for Endometrial Cancer

Age, excess estrogen exposure, hypertension, diabetes, family history, and certain genetic syndromes are well-described risk factors for the development of endometrial cancer (Table 2). Endometrial cancer incidence is low before age 50 and peaks in the 60s. Excess estrogen exposure may be endogenous (early menarche, late menopause, nulliparity, obesity, chronic anovulation) or exogenous (unopposed estrogen therapy, tamoxifen). Hypertension and diabetes have

Table 2 Risk factors for endometrial cancer

Risk factor	Estimated relative risk
Age	2–3
Hypertension	1.3–3
Diabetes	1.3–3
Estrogen exposure Endogenous	
Early menarche	1.5–2
Late menopause	2–3
Nulliparity	3
Obesity	2–5
Chronic anovulation	1.5
Estrogen-secreting tumor	>5
Exogenous	
Unopposed estrogen therapy	10–20
Tamoxifen	2–3
Family history	1.3
Lynch syndrome	6–20

Adopted from ACOG Practice Bulletin Number 149

been shown to be risk factors independent of their association with obesity.

Family history of endometrial cancer appears to confer a slightly higher risk compared to the general population. Lynch (formerly HNPCC) syndrome, an autosomal dominant condition caused by a mutation in a mismatch repair (MMR) gene, is associated with a 40–60 % lifetime risk of endometrial cancer (American Society of Clinical Oncology 2014).

In contrast, the use of hormonal contraceptives – including combined oral contraceptive pills, depot medroxyprogesterone acetate (Depo-Provera®), and levonorgestrel intrauterine device (Mirena®) – *decreases* the risk of endometrial cancer.

4 Etiology

Causes of PMB can be categorized into gynecologic and non-gynecologic (Table 1). The most common gynecologic causes include endometrial polyps (~40 %) and urogenital atrophy (~30 %), followed by endometrial hyperplasia (with or without atypia), uterine cancer, endometritis, and hormone therapy. Leiomyomas (uterine fibroids) could cause PMB, but this is less likely because leiomyomas generally become quiescent after menopause. Although the vast majority of leiomyomas are benign, a malignant leiomyosarcoma should be suspected when a patient presents with PMB and a rapidly enlarging fibroid. Cervical polyps, cervicitis, cervical cancer, and rare, estrogen-secreting ovarian cancer may also cause PMB. Trauma and foreign body in the lower genital tract, when present, would be the source of bleeding. Non-gynecologic causes include urethral caruncles and polyps, urinary tract infections, urologic cancer, diverticulitis, bowel inflammation, gastrointestinal malignancies, and anticoagulation therapy.

5 Diagnostic Evaluation

Evaluation of PMB centers on finding the cause and excluding endometrial hyperplasia or malignancy. An outpatient work-up includes history, physical examination, and endometrial evaluation. A diagnostic Pap test should be included in the initial work-up because cervical cancer also may present with PMB.

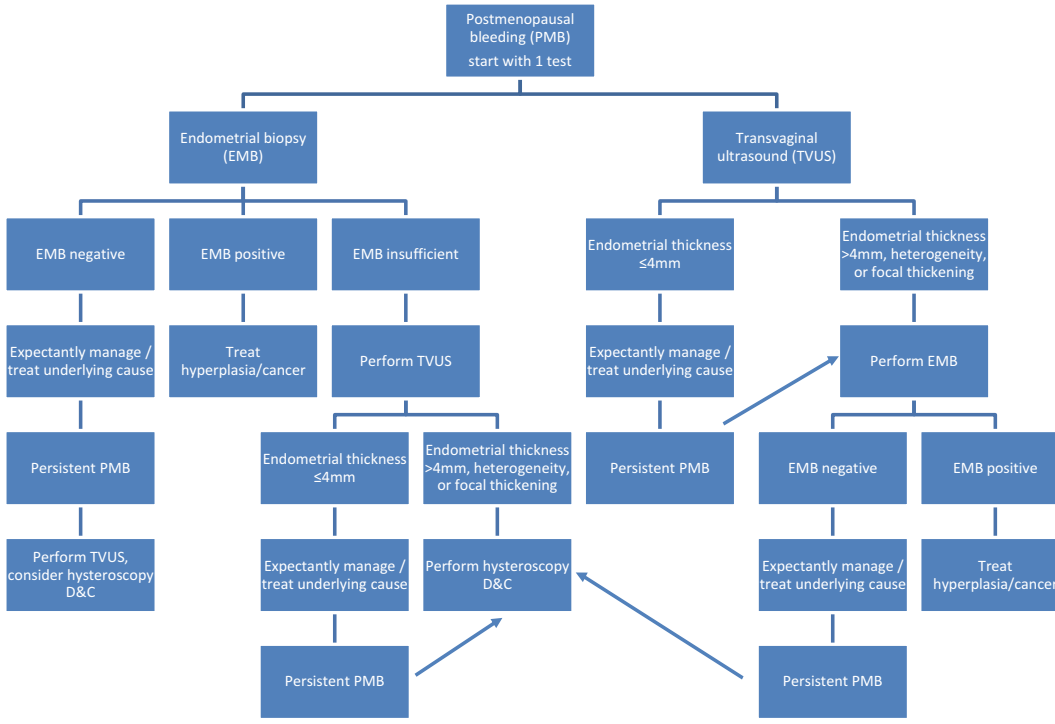

Fig. 1 Endometrial evaluation in postmenopausal bleeding

5.1 History and Physical Examination

A thorough history narrows the differential diagnosis and should cover:

- Onset, quantity, quality, duration, and pattern of bleeding
- Presence of associated symptoms such as weight changes, fevers, abdominal pain, pelvic pressure, and urinary or bowel function disturbances
- Precipitating factors such as trauma
- Use of foreign bodies such as pessaries
- Past medical history and medical comorbidities
- Medications (e.g., hormone therapy, selective estrogen receptor modulators, anticoagulants)
- Family history of endometrial, colon, and breast cancer

A focused examination may localize the source of the bleeding to the lower genital tract and should include inspection of the external genitalia, urethral meatus, vagina and cervix for atrophy, inflammation, lesions, trauma, and foreign body. Bimanual palpation of the upper genital tract should assess the size and contour of the uterus, presence of adnexal masses, and presence of uterine or adnexal tenderness. Additionally, a rectovaginal exam should be performed to assess for rectal masses. Urinalysis and colonoscopy may help differentiate if the source of the vaginal bleeding is non-gynecologic.

5.2 Endometrial Evaluation

Assessment for endometrial malignancy is paramount to the evaluation and is the main diagnostic goal. There are two strategies to evaluate the endometrial lining after an initial episode of PMB – pelvic imaging and/or endometrial biopsy (Fig. 1).

Outpatient endometrial biopsy is a minimally invasive method of obtaining a histopathologic

Table 3 Treatment of postmenopausal bleeding based on diagnosis

Diagnosis	Treatment
Endometrial cancer	Hysterectomy with BSO +/− lymph node dissection
Endometrial hyperplasia	
With atypia	Hysterectomy with BSO[a] Progestin therapy (poor surgical candidates)
Without atypia	Progestin therapy
Leiomyosarcoma suspected	Hysterectomy with BSO
Endometrial or cervical polyp	Hysteroscopy with polypectomy
Urogenital atrophy	
Symptomatic	Vaginal moisturizers or lubricants Vaginal estrogen therapy
Asymptomatic	Expectant management
Endometritis	Doxycycline
Non-gynecologic causes	Appropriate referral

[a]*BSO* bilateral salpingo-oophorectomy

diagnosis. This office procedure is well tolerated and requires little or no anesthesia; thus it has largely replaced the more expensive, operating room-based dilation and curettage (D&C) procedure. While several endometrial suction devices for endometrial sampling exist, the Pipelle® low-pressure endometrial suction curette has been shown in a meta-analysis to have the highest sensitivity of 99.6 % in detecting endometrial cancer and 82 % in detecting endometrial hyperplasia with atypia (Dijkhuizen et al. 2000) with a low complication rate. Endometrial biopsies are not sensitive for diagnosing structural abnormalities such as endometrial polyps and leiomyomas.

An alternative in the initial evaluation is a transvaginal ultrasound (TVUS). TVUS is a non-invasive test that measures the maximal thickness of the endometrial lining from one basalis layer to the opposing layer in the anteroposterior dimension with a sagittal view of the uterus. Fluid within the uterine cavity is excluded from the endometrial thickness measurement. Studies have shown that an endometrial thickness of $\leq$4 mm in symptomatic patients has a sensitivity and specificity of about 95 % and 50 % in detecting endometrial cancer and a negative predictive value of over 99 % in excluding endometrial cancer (Hanegem et al. 2011). An endometrial thickness $>$4 mm does not diagnose endometrial cancer but cannot be used to exclude malignancy. Additionally, the finding of any focal thickening or heterogeneity in the endometrial lining should warrant further evaluation.

The American College of Obstetricians and Gynecologists supports the use of either TVUS *or* endometrial biopsy as the first diagnostic test. TVUS is better tolerated in nulliparous women, women with severe vaginal atrophy, or those with cervical stenosis (American College of Obstetricians and Gynecologists 2009). Both tests do not need to be performed together as the initial diagnostic approach. However, if an initial TVUS shows an endometrial thickness of $>$4 mm, heterogeneity, or focal thickening, then a follow-up endometrial biopsy is indicated. Likewise, if an initial endometrial biopsy is insufficient for diagnosis, then a follow-up TVUS is indicated. Importantly, if an initial TVUS shows the endometrial thickness as $\leq$4 mm but the patient has persistent PMB, an endometrial biopsy should be performed.

When the findings from both TVUS and endometrial biopsy are insufficient to exclude malignancy, a biopsy cannot be performed secondary to cervical stenosis or patient intolerance, or when the patient has recurrent bleeding (even in the setting of a negative endometrial biopsy and reassuring TVUS), the endometrium should be further evaluated with hysteroscopy and D&C.

Hysteroscopy directly visualizes the endometrial cavity for focal lesions and allows for lesion-specific biopsy or excision. D&C allows for the

systematic sampling of the endometrium in all quadrants of the uterine cavity, which cannot be accomplished with a Pipelle aspirator. These procedures may be done concomitantly in the office or in the operating room, depending on provider and patient preference, availability of resources, and anesthesia requirement. Hysteroscopy has the theoretical risk of dissemination of malignant cells by flushing endometrial tissue through the fallopian tubes into the peritoneal cavity during uterine cavity distention, but studies to date have not validated this theoretical concern. Prognosis and survival for women with endometrial cancer who have undergone hysteroscopy prior to their cancer treatment (Ben-Arie et al. 2008; Takac and Zegura 2007) are not worsened. Hysteroscopy remains an important diagnostic tool in women with PMB when indicated.

5.3 Diagnostic Pap Test

All women with PMB should have a diagnostic Pap test performed to assess for cervical cancer, if one has not been performed in the past year, or if there are any concerning findings on physical exam. Abnormal Pap test cytology and subsequent pathology from the colposcopy-directed biopsies (and endocervical curettage) should be managed according to the current American Society for Colposcopy and Cervical Pathology guidelines. The evaluation of the cervix should not preclude or eliminate the evaluation of the endometrial cavity outlined above to exclude endometrial cancer.

6 Management

Management of postmenopausal bleeding ultimately depends on the suspected cause (Table 3).

Diagnosis of endometrial cancer warrants prompt referral to a gynecological oncologist for a total hysterectomy with bilateral salpingo-oophorectomy and possible lymph node dissection. The approach of the hysterectomy (laparoscopic or open) depends upon multiple factors, including prior surgical history, uterine size, comorbidities, extent of disease, and surgeon preference.

Endometrial hyperplasia with atypia found on endometrial biopsy warrants further evaluation with a hysteroscopy and D&C, given the high risk of concurrent endometrial carcinoma (up to 35 %) (Trimble et al. 2006). Treatment of endometrial hyperplasia with atypia once malignancy is excluded should involve a total hysterectomy with bilateral salpingo-oophorectomy, due to the high risk of progression to endometrial cancer (Kurman et al. 1985). Alternatively, patients who are poor surgical candidates may be managed with either oral or localized (Mirena® intrauterine device) progesterone therapy with surveillance endometrial biopsies. Progression to endometrial cancer without treatment is 25–30 %.

Endometrial hyperplasia without atypia is generally treated with either oral or localized progesterone therapy. Progression to cancer for simple hyperplasia without atypia is 1 % and complex hyperplasia without atypia is 3 %. Diagnosis of endometrial hyperplasia (with or without atypia) with no source of exogenous or endogenous estrogen excess warrants evaluation for an estrogen-producing tumor (ovary, adrenal gland), given menopause is an estrogen-depleted state.

When leiomyosarcoma is suspected in the setting of PMB and a rapidly enlarging fibroid, a total hysterectomy with bilateral salpingo-oophorectomy is recommended. The diagnosis of a uterine sarcoma can only be made on histopathology; no imaging test can reliably exclude a leiomyosarcoma. A negative endometrial biopsy is insufficient for excluding a uterine sarcoma, as this type of malignancy is most often found deep to the endometrial lining.

Once hyperplasia and malignancy have been excluded, many cases of PMB tend to be self-limited and may be expectantly managed.

Women with symptomatic urogenital atrophy tend to have vaginal irritation or dyspareunia in addition to light bleeding. Treatment strategies include vaginal moisturizers and lubricants and topical estrogen therapy (vaginal suppositories, rings, creams). Additionally, these patients may benefit from pelvic physical therapy.

Women with PMB secondary to endometrial or endocervical polyp(s) should be counseled for removal of the polyps. The vast majority of

endometrial and endocervical polyps are benign, but malignancy within a polyp is found in approximately 5 % of symptomatic, postmenopausal women. A hysteroscopy with polypectomy can be done in either an office setting under local anesthesia or as outpatient in the operating room, depending on surgeon and patient preference and the extent of polyps.

Women diagnosed with endometritis on endometrial biopsy should be treated with a course of doxycycline 100 mg BID x 7 days.

Patients should be counseled that any persistent or recurrent bleeding should be reported to their physician for further evaluation, even if the initial evaluation was benign. All tests for endometrial evaluation have false-negative rates; therefore further assessment of the endometrium is warranted with a hysteroscopy for direct visualization of the endometrial cavity, directed biopsies, and a thorough curettage of the entire cavity. Moreover, both non-endometrial and non-gynecologic sources of the bleeding should be carefully explored.

7 Conclusion

Postmenopausal bleeding is a common gynecological complaint that warrants a thorough work-up to exclude an endometrial (and cervical) malignancy. Once cancer has been excluded, treatment should be tailored to the specific etiology, ranging from expectant management to topical vaginal estrogen therapy for urogenital atrophy and surgical management for endometrial polyps and endometrial hyperplasia with atypia. Recurrent and persistent bleeding should be managed aggressively.

8 Cross-References

- Benign and Malignant Pathology of the Endometrium
- Endometrial Hyperplasia

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Management of Risks Factors for Older Women: Osteoporosis and Cardiovascular Disease

Katrina Wade and Alexander M. Quaas

Abstract

Osteoporosis and cardiovascular disease are common conditions in older women, with a high prevalence and associated morbidity and mortality after the menopausal transition. Osteoporosis is more common in women than in men, occurring primarily after menopause when estrogen levels drop. Fractures are the most concerning complication of osteoporosis in women, with the hip, vertebrae, and forearm as the most common sites of fracture. Risk factors and non-pharmacologic prevention, diagnosis, and pharmacologic management are reviewed in this chapter. New attitudes toward the use of hormone replacement are also addressed.

Cardiovascular (CV) disease is the leading cause of death for women in the United States. Risk factors for cardiovascular disease are discussed in this chapter, specifically those unique to women such as polycystic ovarian syndrome, menopause, and certain complications of pregnancy.

Keywords

Menopause • Osteoporosis • Cardiovascular disease • Disease prevention • Screening • Hormone replacement • Bisphosphonates • Risk factors • Bone density

Contents

1 Introduction

As life expectancy continues to increase, management of chronic conditions associated with aging in women becomes even more important. Especially after the menopausal transition, women face the risk of the serious and disabling conditions of osteoporosis and cardiovascular disease (CVD). Awareness of risk factors and strategies for primary and secondary prevention are essential for clinicians caring for older women, given the massive public health burden of osteoporosis and CVD on society. Osteoporosis-related fractures

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and cardiovascular events are major causes of morbidity and premature mortality in aging women. Modifiable and nonmodifiable risk factors have been identified for both conditions, some of which are specific to female gender.

1.1 Osteoporosis

1.1.1 Epidemiology

Osteoporosis is a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility (Bouillon et al. 1991). Of the more than ten million people in the United States that have osteoporosis, 80% of those are estimated to be women, most of which are over the age of 50. In fact, the risk of having an osteoporosis-related hip fracture is greater than the risk of developing breast, ovarian, and uterine cancer combined (NOF 2015). For menopausal women over 65, 38% have osteopenia and an additional 20% have osteoporosis. By age 85, only 15% of women still have normal bone density.

One in two women over the age of 50 are estimated to have an osteoporosis-related fracture during their lifetime (NOF 2015).

Chronic bone loss in the spine results in gradual collapse/fracture of the thoracic vertebrae and excessive curvature [kyphosis]. White women have a one-in-six lifetime risk of having a hip fracture (International Osteoporosis Foundation).

Osteoporosis is most commonly seen in Caucasian women or those of Asian descent. About 15% of Caucasian women and 90% of Asian-American women are lactose intolerant making it more difficult to obtain enough calcium in the diet. Caucasian women are estimated to lose on average one-third of the bone density in their hip between the 20 and 80 years of age. Most bone density is lost following menopause when estrogen levels drop. Many African-American and Latina women over the age of 50 also have osteoporosis but to a lesser extent, 5% and 10%, respectively (NOF 2015). Fractures are the most concerning complication of osteoporosis in women. The most common types of fractures include those of the hip, vertebrae, and forearm. These fractures often occur after falls in elderly women (WHO 2004).

The main underlying cause of osteoporosis in postmenopausal women is a result of an imbalance between bone resorption and bone formation. After loss of estrogen in the menopause, excessive bone resorption results in a 1–8% loss of bone density per year. Many women may enter the menopause with osteopenia due to risk factors as shown in Table 1. Bone health counseling begins in adolescence during peak bone building (ACOG 2012) and continues for a lifetime. Women's healthcare providers should counsel their patients about lifestyle factors including smoking, poor nutrition, weight-bearing exercises, and excessive weight loss.

Table 1 Risk factors for osteoporosis: nonmodifiable and potentially modifiable

Nonmodifiable	Potentially modifiable
Female sex	Vitamin D deficiency, calcium deficiency
Advancing age	Excessive alcohol consumption [3 or more/day]
European or Asian race	Tobacco smoking
Family history of fracture or osteoporosis	Malnutrition
Previous fracture	Inactive
Early menopause/hysterectomy/oophorectomy	Heavy metals: aluminum, cadmium, and lead intake
Small stature, slender	High phosphoric acid intake [soft drinks]
Medical disorders: Turner's syndrome, hypothalamic amenorrhea, Cushing's syndrome, hyperthyroidism, malabsorption, diabetes, liver disease, inflammatory bowel disease	Many medicines: proton-pump inhibitors, antiestrogens, steroids, chemotherapy, antiepileptics, excess thyroid, anticoagulants, thiazolidinediones, lithium, GnRH agonists, aromatase inhibitors

As perimenopausal patients enter the menopause, evaluation of lifelong risk factors, correction of potentially modifiable factors, consideration of a bone density study in high-risk patients, and having a risk-benefit discussion regarding estrogen replacement therapy are important to reduce potential fracture risk.

1.1.2 Diagnosis

It is recommended that women should begin screening for osteoporoses at age 65. Postmenopausal women younger than 65 should be screened if they have risk factors or history of adult fracture (ACOG 2012).

Screening tests for bone mineral density (BMD) are most commonly done using dual-energy X-ray absorptiometry (DXA). Results of this test are reported as a T-score, which compares the current bone density to that of a healthy young woman (NIH). T-scores between −1.0 and −2.5 are considered osteopenia and T-scores less than −2.5 are indicative of osteoporosis. Osteoporosis can also be a valid diagnosis even if the patient has a normal T-score if they have a history of frequent bone fractures (NOF 2015). DXA have been shown to have a high specificity but low sensitivity meaning that the risk of fracture is high with a low BMD but should still not be ignored with normal BMD (WHO 2004). DXA also often underestimates BMD in small, thin women with T-scores indicating osteoporosis when BMD is actually normal for their body size (Cosman 2013).

Postmenopausal women make the largest population of individuals with osteoporosis in the United States. This is largely due to the significant reduction in production of estrogen. Estrogen is an important hormone for inhibiting bone resorption. It functions by binding to receptors on osteoblasts to inhibit synthesis of interleukin-6 (IL-6), a potent stimulator of bone resorption. Estrogen also stimulates apoptosis of osteoclasts, the bone cells responsible for bone resorption. Decreased estrogen levels lead to an increase in IL-6 production and increased life-span of osteoclasts. Both of these factors lead to increased bone breakdown and risk of osteoporosis (WHO 2003).

1.1.3 Pharmacologic Management

Prevention of Osteoporosis and Bone Loss

Estrogen-progestin therapy was previously considered to be the best way to prevent postmenopausal osteoporosis. However, the impact of the Women's Health Initiative in 2002 led to a reduction in its use due to concerns regarding breast cancer and heart disease (Rossouw WHI 2002; Anderson WHI 2004; WHO 2004). The more recent identification of significant side effects associated with prolonged bisphosphonate treatment along with better clarification of the WHI studies has resulted in new recommendations for the use of estrogen for prevention of bone loss.

ACOG recommends that the clinician must work closely with the patient to determine what is in her best interest because the risk of HT is smallest in the younger postmenopausal woman and increases with age (ACOG 2012, reaffirmed 2014).

- Hormone therapy [HT] has a beneficial effect on bone health (ACOG 2012).
  - WHI provided a randomized controlled trial that reported a statistically significant 33–36% reduction in hip and vertebral fractures in a "normal" non-osteoporotic population of postmenopausal women (WHI 2002).
  - The Danish Osteoporosis Prevention Study (prospective controlled comprehensive cohort of 2016 women) reported that use of HT for 5 years in recently postmenopausal women

statistically reduced the number of forearm fractures (Mosekilde 2000).
- Hormone therapy is FDA approved for the prevention of osteoporosis in women at increased risk of osteoporosis and fracture.

The last three large, randomized prospective trials reported no increase in breast cancer and were associated with reductions in cardiovascular disease if initiated within early menopause. *These studies are consistent with the multiple prospective cohort studies in 1980 that indicated hormone therapy was associated with a nearly 50% lower risk of coronary heart disease in postmenopausal women* (Keaney 2016).

- WHI 2002 and WHI 2004 reported that there was no increased risk of breast cancer or heart disease [adjusted relative risk confidence intervals used].
  - Follow-up studies reported significant reductions in CVD if started in early menopause (Manson 2007; Hodis 2016).
- 1,006 recently postmenopausal women randomized for a 10-year trial but followed for 16 years. Women using HRT had significantly lower risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of any cancer, venous thromboembolism, or stroke (Schierbeck 2012).
  - Several bisphosphonates are approved for prevention but are currently often reserved for patients with established osteoporosis [due to a widely accepted 3–5-year limitation of use except in specific patients].
- Drug therapy may also be beneficial for women with osteopenia indicated by a T-score between −1.0 and −2.5 and a 10-year >20% estimated risk of osteoporosis-related fracture or >3% estimated risk of hip fracture according to the Fracture Risk Assessment Tool (FRAX) calculator created by the World Health Organization (NOF 2015).

Treatment for Established Osteoporosis

The most common treatment for osteoporosis are the bisphosphonates. The bisphosphonates bind hydroxyapatite crystals on the bone surface and inhibit bone resorption by osteoclasts (Srivastava and Deal 2002). Alendronate, risedronate, and ibandronate are the bisphosphonates currently approved by the FDA. Alendronate and risedronate have been shown to reduce the occurrence of hip and vertebral fractures, while ibandronate has only been shown to reduce the risk of vertebral fracture. The National Osteoporosis Foundation (NOF) recommends the use of bisphosphonates in postmenopausal women with a history of fracture or T-score less than −2.5.

Bisphosphonates are available as pills and taken once per day, week, or month depending on the medication. Oral options include:

- **Alendronate sodium** is available as a daily tablet of 5 mg or weekly tablet of 35 mg. There are also 10 mg daily tablets and 70 mg weekly tablets combined with 2,800–5,600 international units (IU) of vitamin D for prevention in women with previous fractures. A form of alendronate called Bisoto must be dissolved in 4 oz of water and taken on an empty stomach (Cosman et al. 2013).
- Risedronate is available as a 5 mg daily tablet, 35 mg weekly tablet with 500 mg calcium carbonate, 75 mg twice-monthly tablet, and 150 mg monthly tablet.
- Ibandronate sodium is available as a 150 mg monthly tablet.
  - It is recommended that patients take these medications first thing in the morning on an empty stomach with 8 oz of plain water. Patients should wait 60 min before eating,

drinking, or taking any other medication. Delayed-release risedronate should be taken immediately after eating breakfast, and they should wait 30 min before eating, drinking, or taking any other medication. It is also recommended to stay upright for an hour in each case (Cosman et al. 2013). Bisphosphonates can cause gastrointestinal (GI) distress so it is important to follow these guidelines (WHO 2004).

"Estrogen-like" drugs such as tamoxifen and raloxifene have been shown to decrease postmenopausal bone loss but to a lesser extent than bisphosphonates and estrogen. They are described as selective estrogen receptor modulators (SERMs). Tamoxifen is also used in patients with previous breast cancer in order to reduce the risk of recurrence. Studies have shown that raloxifene increases BMD of the lumbar vertebrae, hip, and femur. It has also been shown to decrease the risk of fracture by 50% in women without a prior fracture and 30% in women with a prior fracture. However, raloxifene has been associated with an increased risk of thromboembolism, similar to that seen in treatment with estrogen (Srivastava and Deal 2002).

Injectable or IV options include:

- Ibandronate is also available as a 3 mg injection administered every 3 months
- Zoledronic acid is another bisphosphonate available as a yearly injection of 5 mg in 100 mL. It is offered as an alternative for women who cannot tolerate oral bisphosphonates or would rather receive a once-yearly regimen. It has been shown to decrease the risk of hip and vertebral fractures and reduce the risk of recurrent fractures in women with a recent hip fracture. Injection with zoledronic acid has been shown to cause an acute-phase reaction of arthralgia, headache, myalgia, and fever in 32%, 7%, and 3% of patients upon first, second, and third injection, respectively. Pretreatment with acetaminophen should decrease these symptoms (Cosman 2013; Lyles 2007).
- Denosumab is another available treatment for patients who cannot tolerate or do not respond to bisphosphonate therapy. It is an antibody against the factor RANKL which is involved in development of osteoclasts. It has been shown to improve BMD and reduce fracture risks in postmenopausal women. Patients taking denosumab sometimes present with decreased blood calcium levels. Therefore, it is contraindicated in patients with kidney disease or a prior reduction in blood calcium levels. Low blood calcium levels can, however, be corrected by increasing calcium and vitamin D intake. Denosumab is administered through a 60 mg subcutaneous injection every 6 months by a healthcare professional. There is a small risk of cellulitis and eczema following administration (Cosman 2013).

Calcitonin and parathyroid hormone (PTH) are also offered for treatment of postmenopausal osteoporosis. PTH works directly by stimulating bone formation unlike the other drug therapies that only prevent bone resorption. PTH is available as a preparation called teriparatide, which is administered as a 20 μg daily subcutaneous injection in patients with severe osteoporosis for 2 years. It is effective in increasing vertebral bone density and is more effective than any other treatment in reducing the risk of vertebral fracture. However, this drug is very expensive and therefore only offered for patients with severe osteoporosis and a history of hip or vertebral fracture (WHO 2003). On the other hand, calcitonin works with PTH to regulate calcium levels in the body. It has not been shown to improve BMD anywhere besides the vertebrae, but it is often used immediately following vertebral fractures due to its analgesic properties. It is administered as either a nasal spray or injection. Treatment usually only lasts until pain symptoms have subsided when patients are switched to more effective long-term therapy (Cosman 2013).

1.1.4 Risk Factors and Non-pharmacologic Prevention

Prevention is the key when it comes to osteoporosis. Adolescent girls reach their peak bone mass at the conclusion of skeletal maturation which is usually at the end of puberty. Studies have shown that a 10% increase in peak bone mass reduces the risk of hip fracture by 30%. Therefore, it is of much interest to find ways to increase peak bone mass in adolescent girls to prevent osteoporosis later in life (WHO 2003). American College of Obstetrics and Gynecology recommends that bone health counseling begins in adolescents.

Peak bone mass is influenced by a variety of factors including heredity, sex, diet, exercise, and exposures (Table 1). Twin studies indicate that genetics account for up to 50% of the variation in BMD in the population. Heritability of peak bone mass is likely polygenic, and the effects of these genes vary depending on the skeletal site. Women also tend to have a lower peak bone mass than men which is attributed to a decrease in the period of bone maturation following puberty in women as compared to men (WHO 2003).

Environmental factors including diet, exercise, and exposure to risk factors also greatly affect peak bone mass as well as the rate of decline in BMD during one's lifetime (Table 1). Deficiencies in calcium, vitamin D, and protein have been associated with decreased bone grown and accelerated bone loss. Deficiencies in these nutritional components are common in elderly women due to a reduction in dairy consumption, a decreased absorptive capacity of the intestinal epithelium, and an impairment of the kidneys to resorb calcium and respond to PTH. Elderly individuals are also not able to produce as much vitamin D and often reduce their sun exposure. All of these factors contribute to a decrease in BMD putting this population at higher risk for developing osteoporosis (Srivastava and Deal 2002). Protein deficiency has also been associated with decreased BMD and increased risk of fracture. This is likely also due to a decrease in muscle mass resulting in impaired coordination and balance which increases the risk of having a fall. Other nutritional components including vitamin K, phosphates, magnesium, and other trace elements have also been shown to be important in decreasing bone loss (WHO 2003).

It is recommended that premenopausal women consume 1,000 mg of calcium per day, and postmenopausal women should consume 1,200–1,500 mg per day. Calcium supplements are often suggested for postmenopausal women. Experts also recommend that postmenopausal women consume 800 IUs of vitamin D per day. This also often requires supplementation. Premenopausal women should consume 600 IUs of vitamin D per day. Furthermore, protein supplements may also be recommended in postmenopausal women with history of a fracture (NIH 1994).

Exercise is another major component in increasing bone density and decreasing bone loss. Exercise not only increases bone strength but also improve muscle strength and coordination which reduces the risk of falling. Weight-bearing exercises have been shown to be the most effective at increasing bone mass and preventing age-related bone loss (Srivastava and Deal 2002). Women should be encouraged to engage in 30 min of weight-bearing exercise three times per week (Cosman 2013). Exercise has also been shown to help decrease pain and improve functional capacity in women with a previous fracture. It also decreases the risk of future fractures. However, women with vertebral fractures should use caution when performing some exercises, especially those involving spinal flexion, so they do not develop new fractures (Srivastava and Deal 2002).

Other risk factors for osteoporosis include tobacco use and excessive alcohol consumption. Studies have linked tobacco use with a decrease in bone density, bone healing, and bone formation (Table 1). In postmenopausal women, tobacco is thought to increase estrogen metabolism resulting in a longer life for osteoclasts which function to break down bone. Studies have also suggested that tobacco users typically have lower body weights, nutritional deficiencies, and decreased physical activity which contribute to the increased risk of osteoporosis. Postmenopausal women who use tobacco have been shown to lose cortical bone

50% faster than postmenopausal women who do not use tobacco. Excessive alcohol consumption (>3 drinks/day) has also been associated with an increased risk of osteoporosis. Although the exact mechanism of action of alcohol on the bone is poorly understood, excessive alcohol consumption is thought to have the greatest effect on bone formation. Therefore alcoholism earlier in life is likely to have adverse consequences for older women. Excessive alcohol consumption will decrease the peak bone mass making even smaller amounts of bone loss more detrimental. Excessive alcohol consumption in elderly women has also shown to increase bone loss. Like tobacco use, excessive alcohol use is often associated with nutritional deficiencies, decreased calcium absorption, and physical inactivity which likely contribute to such bone loss. Intoxication also causes a loss in coordination and balance which increases the risk of falling and have a fracture. On the other hand, light to moderate alcohol consumption have not been associated with an increased risk of osteoporosis (Sampson 2003).

Some medications can also increase bone loss. The most widely known are glucocorticoids (or steroids) which are used to reduce inflammation in conditions such as rheumatoid arthritis, Crohn's disease, lupus, and asthma (Table 1). Taking steroids pills at a 5 mg dosage for longer than 3 months greatly increases the risk of developing osteoporosis. Therefore, healthcare providers should use steroids only when absolutely necessary and should use the lowest dose possible for the shortest time. Patients should also ensure they consume adequate amounts of calcium and vitamin D as well as exercise regularly and refrain from smoking while taking steroids. Other medications associated with bone loss include aluminum-containing antacids, antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, primidone), aromatase inhibitors, chemotherapeutic drugs, gonadotropin-releasing hormone, cyclosporine, heparin, lithium, medroxyprogesterone acetate, methotrexate, proton-pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), thiazolidinediones, tamoxifen (premenopausal use), and thyroid hormones in excess. Similar precautions should be taken when using these medications (NOF 2015).

1.2 Cardiovascular Disease

1.2.1 Background

Cardiovascular (CV) disease is the leading cause of death for women in the United States, killing approximately 290,000 women annually or one in every four female deaths. Although CV disease is sometimes thought of as a "man's disease," around the same number of women and men die each year of heart disease in the United States. Despite increases in awareness over the past decade, only 54% of women recognize that CV disease is their number one killer. CVD and stroke are the most frequent causes of death in women. Knowledge among women themselves has improved (from 30% to 56% from 1997 to 2012), but this still leaves approximately half of women unaware that they are at highest risk of dying from heart disease or stroke as opposed to other causes, such as cancer (Table 2).

Almost two-thirds (64%) of women who die suddenly of coronary heart disease have no previous symptoms. Women tend to present for chest pain evaluation in the emergency room at a greater rate compared to men (4.0 million visits for women vs 2.4 million visits for men). However, women tend to present with less typical symptoms, such as fatigue sleep disturbance and shortness of breath, back pain, indigestion, weakness, and nausea/vomiting. Thus, women are frequently a clinical challenge for the cardiologist, and their symptom misinterpretation may lead to the wrong diagnosis and treatment with potentially unfavorable consequences.

Intensive preventative efforts across a woman's life-span and appropriate diagnostic efforts later in life are essential to minimize the current high rates of morbidity and mortality of CV disease in women. Direct and indirect costs of heart disease total more than $320.1 billion, including health expenditures and lost productivity. This highlights CV disease as an important public health challenge.

Table 2 Causes of death in women

	Women (%)	Men (%)
Heart disease + stroke	29.7	29.1
Heart disease	23.5	24.9
Cancer	22.1	24.4
Stroke	6.2	4.2
Chronic lower respiratory disease	5.9	5.3
Alzheimer disease	4.7	2.1
Unintentional injuries	3.6	6.2
Diabetes	2.7	2.9
Suicide	0.7	2.5
Influenza and pneumonia	2.1	1.9
Kidney disease	2.1	2.0
Septicemia	1.5	1.3

From Centers for Disease Control. Deaths, percent of total deaths, and death rates for the 15 leading causes of death in selected age groups, by race and sex: United States, 2011. Available at: http://www.cdc.gov/nchs/data/dvs/LCWK3_2011.pdf.

1.2.2 Risk Factors: Prevention and Interventions

Traditional and nontraditional risk factors (Table 3) contribute to the development of CV disease in both women and men, but some risk factors are more unique to women (e.g., pregnancy-related complications) or selectively disadvantage women (e.g., depression) (Wenger reference). Clinicians have traditionally relied on the Framingham Risk Score to assess CV disease risk; however, this risk assessment underestimates the risk in women and classifies 90% of women as low risk. The 2013 ACC/AHA guidelines on the assessment of CV disease recommend estimating 10-year or lifetime CV disease risk from a pooled cohort of equations that take into account such factors as race and sex (Goff 2013).

Hypertension

Underdiagnosed and undertreated hypertension remains a major risk factor for CHD in women. The prevalence of hypertension in women and men continues to increase, and it is estimated that lifetime risk of developing hypertension is approximately 90%. Hypertension significantly increases the risk of myocardial infarction, heart failure, atrial fibrillation, stroke, and renal failure. Premenopausal women are at a higher risk of hypertensive end-organ damage than age-matched men, including microalbuminuria and left ventricular hypertrophy. Blood pressure (BP) increases during the menopausal transition may be related to the decline in estrogen levels, which leads to upregulation of the renin-angiotensin system, production of vasoconstrictive factors such as endothelin, and increased salt sensitivity.

Over the age of 65 years, hypertension prevalence is higher in women than men, but less than half receive adequate treatment. Lifestyle modifications can prevent hypertension. Control of hypertension decreases both the risk of stroke and that of fatal and nonfatal coronary events and heart failure.

Table 4 outlines the recommendations for the management of hypertension from the panel members appointed to the Eighth Joint National Committee (JNC 8).

Cholesterol

Elevated cholesterol, specifically low-density lipoprotein (LDL), is a major cause of heart disease. In addition to heart-healthy lifestyle modifications, the primary pharmacologic therapy is a statin. Traditionally clinicians have treated patients with statin therapy to a certain target, an LDL goal of below 100 mg/dL in those at high cardiovascular risk and a goal of 70 mg/dL or lower for patients at very high risk. In November of 2013, the American College of Cardiology and American Heart Association (ACC and AHA)

Table 3 Risk factors of cardiovascular disease

Traditional
Hypertension
Hyperlipidemia
Tobacco use
Diabetes
Peripheral arterial disease
Chronic kidney disease
Physical inactivity
Obesity
Metabolic syndrome
Genetic, family history
Age
Psychological factors
High stress
Acute mental illness
Depression
Anxiety anger/stress
Marital status
Socioeconomic status
Other
Elevated C-reactive protein/systemic autoimmune disorders/anemia
Menopause/oophorectomy
Polycystic ovary syndrome
Gestational diabetes/hypertension/preeclampsia
Obstructive sleep apnea
Radiation/chemotherapy
Excessive alcohol consumption [>1 drink/day women, >2 drinks/day men]

released updated clinical practice guidelines on reducing cardiovascular risk, which emphasized a move away from specific cholesterol treatment targets and focused in on the intensity of statin therapy for four "major statin benefit groups" (Stone 2013).

Groups benefitting from statin therapy ("statin benefit groups")

The ACC/AHA panel found in its review of statin RCTs that there was a consistent reduction in ASCVD events from statin therapy in both secondary and primary prevention. The intensity of statin therapy was defined based on the average expected LDL-C response. Three types of statin therapy include high intensity (≥50% reduction in LDL-C), moderate intensity (30 to <50% reduction), and low intensity (<30% reduction). The guideline found four major groups where the benefit of a statin on ASCVD risk reduction outweighed the risk of adverse events:

1. Patients with clinical ASCVD (e.g., acute coronary syndromes, history of MI, stable or unstable angina, stroke, transient ischemic attack, or peripheral arterial disease)
2. Patients with primary elevation of LDL-C of 190 mg/dL or higher
3. Patients with diabetes (type 1 and 2) aged 40–75 years with LDL-C of 70–189 mg/dL and without clinical ASCVD
4. Patients without diabetes or clinical ASCVD and estimated 10-year ASCVD risk of 7.5% or greater

For primary prevention, in patients aging 40–75 years with LDL-C of 70–189 mg/dL without diabetes or clinical ASCVD, the decision to initiate statin is based on 10-year ASCVD risk using new pooled risk equations (discussed previously). The data used to identify who would benefit from a statin was based on three trials (Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS-TexCAPS] (Downs 1998), Primary Prevention of Cardiovascular Disease with Pravastatin in Japan [MEGA] (Nakamura et al. 2006), and Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin Trial [JUPITER]) (Ridker 2008) that included patients with LDL-C of greater than 70 mg/dL and less than 190 mg/dL in primary prevention. It was determined that patients with an ASCVD risk of 7.5% or higher benefited most from moderate- to high-intensity statin therapy. This value is not an absolute threshold to start statin therapy, but this is when physicians and patients should engage in discussion of the risks and benefits of statin therapy.

In patients with a 10-year ASCVD risk of 5.0–7.4%, a similar amount of evidence supports moderate- to high-intensity statin therapy, although there is evidence that the benefit of a moderate-intensity statin outweighs the risk of adverse events in this group. For patients with an

Table 4 Recommendation for the management of hypertension

Recommendation 1. The guideline recommends the initiation of drug therapy in order to lower a systolic BP (SBP) of ≥150 mmHg or a diastolic BP (DBP) of ≥90 mmHg for the general population at 60 years of age or older (Grade A). A corollary recommendation is that patients whose achieved SBP on pharmacologic therapy is lower than the new guideline recommendation can be continued at that level of therapy, if well tolerated (Grade E)
Recommendation 2. The target DBP to start pharmacologic therapy for subjects younger than 60 years of age is ≥90 mmHg. On the basis of available evidence, the recommendation for patients aged 30–59 years is strong (Grade A). For those between the ages of 18 and 29, the recommendation is on the basis of expert opinion (Grade E)
Recommendation 3. The target SBP to start pharmacologic therapy for subjects younger than 60 years of age is ≥140 mmHg (Grade E)
Recommendation 4. In the population aged 18 years or older with chronic kidney disease, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to a goal of SBP <140 mmHg and a goal of DBP <90 mmHg (Grade E)
Recommendation 5. The target blood pressure in beginning pharmacologic therapy for the diabetic population aged 18 years or older is <140 mmHg for SBP and <90 mmHg DBP (Grade E)
Recommendation 6. Initial drug therapy for nonblack patients (including diabetic patients) should include a thiazide-type diuretic, a calcium channel blocker, an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (Grade B)
Recommendation 7. Initial drug therapy for black patients should include a thiazide-type diuretic or a calcium channel blocker. This includes patients with diabetes mellitus (Grade B; for diabetic black patients, Grade C)
Recommendation 8. For patients 18 years and older with chronic kidney disease, initial or additional therapy should include an ACE inhibitor or angiotensin receptor blocker, regardless of race or diabetic status (Grade B)
Recommendation 9. An algorithm for managing patients who do not achieve control within 1 month is recommended. If the goal is not achieved, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6. A third drug should be added if the goal is not achieved with two drugs. Drugs from other classes can be used if the target is not achieved with the recommended classes or if there is a contraindication to one of the recommended drug classes. ACE inhibitors should not be combined with angiotensin receptor blockers in the same patient. Referral to an HTN specialist should be considered in complicated cases or in the event of inability to control BP (Grade E)

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ASCVD risk of less than 5% or those not in a statin benefit group (i.e., age <40 or age >75), it is important to consider the risks and benefits of statin therapy as well as considering other risk factors that may better inform treatment decisions such as:

- LDL-C of 160 mg/dL or greater
- Family history of premature ASCVD with onset less than 55 years old in first-degree male relatives or less than 65 years old in first-degree female relatives
- Coronary artery calcium score of 300 Agatston units or more or greater than 75th percentile
- Highly sensitive C-reactive protein of 2 mg/L or greater
- Ankle-brachial index of less than 0.9
- High lifetime risk at age 20–59 years

Table 5 outlines the US Preventive Services Task Force screening recommendations for cardiovascular disorders in women.

2 Risk Factors Unique to Women

2.1 Polycystic Ovarian Syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age. It is a heterogeneous disorder of uncertain etiology, but there is strong evidence that complex interactions between genetic, environmental, and behavioral factors contribute to causing this syndrome. Women with PCOS have an increased risk of presenting with insulin resistance (IR), impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM2), obesity, dyslipidemia, and ultimately CVD.

Table 5 US Preventive Services Task Force screening recommendations for cardiovascular disorders in women

Screening test	Recommendation	Grade
Abdominal aortic aneurysm (AAA)	Women ages 65–75 years who have ever smoked: current evidence is insufficient to assess the balance of benefits and harms of screening for AAA in women ages 65–75 years who have ever smoked	I
	Women who have never smoked: recommends against routine screening for AAA in women who have never smoked	D
Aspirin for the prevention of cardiovascular disease	Women age 55–79: recommends the use of aspirin for women age 55–79 years when the potential benefit of a reduction in ischemic stroke outweighs the potential harm of an increase in gastrointestinal hemorrhage	A
	Women 80 years and older: current evidence is insufficient to assess the balance of benefits and harms of aspirin for CVD prevention in women 80 years or older	I
	Women younger than 55: recommends against the use of aspirin for stroke prevention in women younger than 55 years	D
Blood pressure	Recommends screening for high blood pressure in adults 18 and over	A
Carotid artery stenosis	Recommends against screening for asymptomatic carotid artery stenosis in the general adult population	D
Coronary heart disease (CHD): screening using nontraditional risk factors	Women with no history of CHD: current evidence is insufficient to assess the balance of benefits and harms of using nontraditional risk factors studied to screen asymptomatic women with no history of CHD to prevent CHD events	
	Nontraditional risk factors included in this recommendation are high-sensitivity C-reactive protein (hs-CRP), ankle-brachial index (ABI), leukocyte count, fasting blood glucose level, periodontal disease, carotid intima-media thickness (carotid IMT), coronary artery calcification (CAC), score on electron-beam computed tomography (EBCT), homocysteine level, and lipoprotein(a) level	
Screening with electrocardiography	Women at low risk: recommends against screening with resting or exercise electrocardiography for the prediction of CHD events in asymptomatic women at low risk for CHD events	D
Obesity	Recommends offering or referring adults who are overweight or obese and have additional CVD risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention	B
Cholesterol	Women 45 and older at increased risk for CHD: recommends screening women aged 45 and older for lipid disorders if they are at increased risk for CHD	A
	Women 20–45 at increased risk for CHD: recommends screening women aged 20–45 for lipid disorders if they are at increased risk for CHD	B
Vitamin supplementation	Current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamins for the prevention of CVD	I
	Recommends against the use of beta-carotene or vitamin E supplements for the prevention of CVD	D
Tobacco use	Recommends that clinicians ask all adults about tobacco use and provide tobacco cessation interventions for those who use tobacco products	A

(*continued*)

Table 5 (continued)

Screening test	Recommendation	Grade
Diabetes	Women with elevated blood pressure: recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mmHg	B
	Women without elevated blood pressure: current evidence is insufficient to assess the balance of benefits and harms to screening for type 2 diabetes in asymptomatic women with blood pressure of 135/80 mmHg or lower	I

http://www.uspreventiveservicestaskforce.org/BrowseRec/Index/browse-recommendations Accessed 7/22/15
Grade Definitions
A: Recommends the service. There is high certainty that the net benefit is substantial
B: Recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate or substantial
C: Recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small
D: Recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits
I: Current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined

After making a diagnosis of PCOS, women should have a more aggressive CVD risk factor management (Salley 2007):

- BP and BMI measured regularly, per usual guidelines.
- Lipids measured at diagnosis (this is likely earlier than otherwise indicated).
- Oral glucose tolerance test, if possible, or fasting glucose and hemoglobin A1C measured at diagnosis. If a woman has impaired glucose tolerance, then screen for diabetes every year. If she has normal glucose tolerance, then screen for diabetes at least every 2 years and more often if other risk factors are present.

2.2 Menopause

Menopause is a risk factor for cardiovascular disease (CVD); evidence suggests that the decrease in estrogen experienced has a detrimental effect on cardiovascular function and metabolism. In a review by Mendelsohn and Karas (2005), estrogens have been shown to influence factors involved at every stage of the atherogenic process. These stages include endothelial injury, plaque initiation, inflammation, and plaque rupture and thrombosis.

The effect of hormone therapy on cardiovascular risk is a complex topic and still evolving. Before the Women's Health Initiative (WHI) hormone trials, evidence favored the concept that postmenopausal hormone treatment protected against CVD. Results of the large randomized placebo-controlled WHI estrogen-plus-progestin and estrogen-alone trials found no evidence of CVD protection in women aged 50–79 years, decreased fracture but increased deep vein thrombosis, leading to the conclusion that postmenopausal hormone use may cause more harm than good (Rossouw 2002; Anderson 2004).

However, subgroup analyses of this WHI data provide support **that timing of postmenopausal hormone treatment may be important**. In the estrogen-plus-progesterone trial, a nonsignificant trend toward cardiovascular protection was seen in women who were <10 years postmenopausal, whereas significant excess risk occurred in women >20 years postmenopausal. Similarly, in the estrogen-only trial, there was a trend for cardiovascular protection in women 50–59 years old but increased risk in women >70 years old.

The current state of knowledge regarding the clinical effects of postmenopausal hormone use on risk of CVD events, and risk-benefit ratios, remains controversial and in flux, and this situation is unlikely to change in the near future. More information is needed regarding effects on both potential risks and benefits of hormone therapy by age and menopausal duration. At this time, data remain insufficient to support the use of postmenopausal hormone therapy to reduce the risk of CVD.

2.3 Pregnancy Complications

Common pregnancy complications such as gestational hypertension/preeclampsia and gestational diabetes are associated with an increased risk of CVD later in life.

- Gestational hypertension/preeclampsia – Gestational hypertension and preeclampsia occur in approximately 6–8% of pregnancies. Preeclampsia confers a fourfold increased risk of hypertension later in a woman's life and doubles future stroke risk. The Cardiovascular Health After Maternal Placental Syndromes (CHAMPS) trial demonstrated a 12-fold increased risk of CVD in women who had a pregnancy complicated by preeclampsia (Ray 2005). The presence of multiple risk factors has an additive effect on a women's risk of developing CVD.
- Gestational diabetes – Gestational diabetes affects up to 5% of pregnancies and is associated with an increased risk of CVD later in life. Gestational diabetes confers a sevenfold increased risk of developing type 2 diabetes in the postpartum period (Bellamy 2009). The postpartum development of type 2 diabetes is the predominant driver of the later development of CVD in women with a history of gestational diabetes.
- Preterm delivery – Preterm delivery has been shown to be an independent risk factor for subsequent long-term cardiovascular morbidity and cardiovascular-related hospitalizations (adjusted HR 1.4, 95% CI 1.2–1.6). Patients after a preterm delivery may benefit from cardiovascular risk screening, early detection, and perhaps secondary prevention of CVD (Kessous 2013).
- Multiple miscarriages – Women who experience spontaneous pregnancy loss are at a substantially higher risk of myocardial infarction (MI) later in life. Recurrent miscarriage and stillbirth are strong sex-specific predictors for MI and thus should be considered as important indicators for cardiovascular risk factors monitoring and preventive measures. Pregnancy loss and CVD share common risk factors (Kharazmi 2011).

3 Conclusion

Clinicians should be aware of the high prevalence of osteoporosis and cardiovascular disease in aging women and the high morbidity and mortality associated with these conditions.

Awareness of risk factors for these conditions can assist with diagnosis and with strategies for primary and secondary prevention. Risk factors specific to women are of special importance and outlined in this chapter. Counseling regarding reduction of risk factors for both osteoporosis and cardiovascular disease should begin in young, adolescent patients and last a lifetime. Healthcare providers should evaluate perimenopausal and early menopausal women for osteoporosis and CVD risk factors and recommend appropriate diagnostic studies. For women at risk, consideration of hormone replacement with an individual risk-benefit analysis is appropriate.

4 Cross-References

▶ Management of Menopausal Symptoms
▶ Menopausal Hormone Therapy

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Menopausal Hormone Therapy

Benjamin J. Barenberg and Stephanie D. Pickett

Contents

Abstract

Menopause is associated with physical changes secondary to the loss of estrogen, including hot flushes, vaginal dryness, and bone demineralization that may have a profound impact on a woman's quality of life. With the aging population, management of climacteric symptoms will become routine in gynecologic practice. The purpose of this chapter is to review the physiology of perimenopause, to discuss the appropriate use of hormonal therapy for management of menopausal symptoms, to discuss other benefits afforded from hormonal replacement therapy (HRT), and to discuss considerations for special populations when using hormonal therapy.

Keywords

Hormones • Hormone replacement therapy • Bioidenticals • Menopause • Estrogen

1 Introduction

With the continued aging of the US population, managing the perimenopausal transition and subsequent menopause will be an important component to providing the complete scope of women's health. Menopause is associated with physical changes secondary to the loss of estrogen, including hot flushes, vaginal dryness, and bone demineralization that may have a profound impact on a woman's quality of life. Although non-hormonal

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approaches are available, management of climacteric symptoms can be addressed most effectively through the use of hormonal therapies. The purpose of this chapter is to review the physiology of perimenopause, to discuss the appropriate use of hormonal therapy for management of menopausal symptoms, to discuss other benefits afforded from hormonal replacement therapy (HRT), and to discuss considerations for special populations when using hormonal therapy.

2 Physiology of Perimenopausal Transition

The perimenopausal transition is objectively defined by menstrual irregularity due to the gradual cessation of normal ovulatory function which culminates in menopause, a period in which a woman has permanent cessation of menstruation. Clinically, the diagnosis of menopause is made retrospectively after a patient has experienced a one year menses free interval (Practice Bulletin No. 141 2014). In the late third decade of life, women begin to experience accelerated follicular depletion, and as women begin their fourth decade of life, anovulation becomes more frequent. Accelerated follicular loss is secondary to an increased follicle stimulating hormone (FSH), an increase in luteinizing hormone (LH), and a decrease in inhibin which is responsible for negative feedback on FSH in the pituitary. As women approach 1000 remaining follicles, they will transition into menopause. The median age of menopause in the United States is 51 years old. FSH and LH levels may provide additional evidence when correlated with a clinical history that a patient has completed the menopausal transition. The transition is marked by an elevation in serum FSH, normal serum LH, and a slightly elevated estradiol. Although levels may fluctuate during perimenopause, FSH $>$ 20 IU/L and LH $>$30 IU/L are indicative of permanent cessation of follicular development (Fritz and Speroff 2011). Estradiol alone is not a reliable biomarker to assess for the menopausal transition as estradiol levels will fluctuate throughout the perimenopause (Fritz and Speroff 2011).

3 Climacteric Symptoms

Vasomotor symptoms, vaginal dryness, and sleep disturbances are associated with the menopausal transition (Dennerstein et al. 2000). Vasomotor symptoms are commonly referred to as hot flushes and are most common in late menopause with a prevalence of 65 % (4). Hot flushes are described as a sense of warmth and perspiration over the upper torso and face. Studies are inconsistent regarding risk factors for hot flushes, but studies do consistently show that smoking is associated with an increased risk (Gold et al. 2000). The physiologic mechanism of hot flushes and the role of endogenous estrogen are not completely understood. Luckily the discomfort associated with hot flushes is transient with 50 % of flushes resolving within 6 months and 90 % resolving within 5 years (Kronenberg 1990).

Approximately, 30–50 % of menopausal women report vaginal symptoms including dryness, itching, and dyspareunia (Dennerstein et al. 2000). Unfortunately, these symptoms do not improve over time and may actually exacerbate with increasing age. Approaches to management of climacteric symptoms include hormonal and non-hormonal therapies. The following section will address patient selection and options for hormonal therapies to address climacteric symptoms.

4 Types of Hormone Replacement Therapy

Hormone replacement therapy can be considered for healthy women who are experiencing symptoms of menopause. Treatment should be initiated within 10 years of menopause and contraindications to treatment should be based upon the individual. Before the age of 60, the benefits of HRT are more likely to outweigh the risks. Any changes to the medical or surgical history should prompt a discussion, and risks and benefits of continued HRT should be discussed annually. Side effects of breast tenderness, vaginal bleeding, bloating, and headaches should also be

Table 1 Estrogen-only oral products

Ingredient	Product name	Available dosage (mg/day)
17β-estradiol	Estrace	0.5, 1.0, 2.0
Conjugated equine estrogen	Premarin	0.3, 0.45, 0.625, 0.9, 1.25
Conjugated synthetic estrogen	Enjuvia	0.3, 0.45, 0.9, 1.25
Esterified estrogen	Menest	0.3, 0.625, 1.25, 2.5
Estropipate	Ortho-Est	0.75, 1.5, 3

reviewed with the patient. Treatment can be continued if women over age 60 experience symptoms, but risks of sustained HRT should be discussed and the patient should be under continued clinical supervision. Overall, the goals should be the lowest dose of HRT for the shortest duration needed to manage menopausal symptoms. Short-term therapy for the purposes of HRT is considered 2–3 years. The decision to discontinue HRT should be made on an individual basis, and there is no evidence to support abrupt discontinuation compared to tapering medication to prevent the recurrence of symptoms.

There are benefits to using hormone replacement therapy, with the primary benefit being the alleviation of hot flashes and night sweats. Additionally, vaginal dryness and atrophic changes to the vaginal epithelium improve with the use of estrogen, and quality of life and sexual function benefits have been noted from alleviating these symptoms of menopause. In women under 60 years of age or within 10 years of menopause, HRT can prevent osteoporosis related fractures (Kronenberg 1990). In this population, estrogen-only HRT may also decrease coronary heart disease and all-cause mortality (Kronenberg 1990). Long-term use of HRT is no longer recommended solely for disease prevention.

The risk of breast and ovarian cancer as it relates to HRT is a complex issue with conflicting data. Estrogen therapy alone is associated with an increased risk of venous thromboembolism (VTE) of approximately 1.2–1.5-fold relative risk compared to that of nonusers (Committee Opinion No. 556 2013). Most investigations relating hormone therapy to VTE have been based on orally administered estrogen. The hazard ratio for a stroke is 1.39 and again this is based on data of oral estrogen which undergoes first pass metabolism in the liver leading to higher doses of systemic estrogen than vaginally delivered estrogen (Anderson et al. 2014). These risks overall are generally considered low but can increase with additional risk factors like age, obesity, fractures, and thrombophilic disorders.

While endometrial biopsy is not routinely recommended before initiating HRT, any undiagnosed abnormal uterine bleeding is a contraindication to HRT. Other contraindications to HRT include any estrogen-dependent cancer, suspected pregnancy, history of any VTE, stroke, myocardial infarction, or liver disease (Martin and Barbieri 2014).

4.1 Estrogen Therapy and Estrogen–Progestin Therapy

A variety of modalities for hormonal delivery have been developed. Estrogen alone is appropriate for women who have already undergone a hysterectomy. If the uterus is still in situ, a combination of estrogen and progestin is essential to reduce the risk of endometrial hyperplasia and endometrial cancer. All routes of estrogen are equally effective in alleviating menopausal symptoms. A trial of 3 to 6 months on any of these medications is recommended to determine if symptom relief is adequate prior to changing the dosage or medication type.

4.2 Oral Therapy

Oral HRT has historically been the most popular preparation and was used in the Women's Health Initiative (WHI) studies. Oral therapy has the

Table 2 Combined estrogen–progestin oral products

Ingredient	Product name	Available dosage (mg/day)
Conjugated equine estrogen/medroxyprogesterone	Prempro	0.3/1.5, 0.45/1.5, 0.625/2.5, 0.625/5
17β-estradiol/norgestimate	Prefest	1/0.09
Estradiol/norethindrone acetate	Activella	0.05/0.1, 1/0.5
	Mimvey	0.05/0.1, 1/0.5
	FemHRT	0.0025/0.5
	Jinteli	0.005/1
Estradiol/drospirenone	Angeliq	0.5/0.25, 1/0.5

benefit of improving lipid profiles, but the long-term benefits of this are not clear (Martin and Barbieri 2014). Oral estrogen also increases sex hormone binding globulin (SHBG), triglycerides, C-reactive protein, and thyroid-binding globulin (TBG). Increases in SHBG theoretically could have negative effects on libido as more SHBG leads to less free testosterone. Increased TBG may lead to necessary increases in thyroid medication to keep the patient euthyroid. Oral formulations are available with estrogen only (Table 1) and in combined estrogen–progestin (Table 2) formulations. Generic versions are available for many of these medications.

Patients need to be aware that oral therapy is subject to first pass in the liver that can change the total serum concentration of hormone. Estrogen dose needs to be increased for patients taking anticonvulsants like phenytoin and carbamazepine. Additionally, diabetics taking sulfonylureas may also require increased doses of estrogen. Alternatively, patients who are taking medications for gastroesophageal reflux (cimetidine and omeprazole), antifungals (ketoconazole and fluconazole), and certain antibiotics (erythromycin, sulfonamides, ciprofloxacin) may need to decrease their dosage as these medicines slow the liver's metabolism of estrogen. Alcohol consumption can also alter the metabolism in either direction, so a thorough social history should be obtained.

4.3 Transdermal

Many women like transdermal preparations for their convenience. The transdermal preparations are made with 17β-estradiol, which is the main estrogen secreted by the ovary in premenopausal women (Martin and Barbieri 2014). Transdermal regimens cause less of an effect on SHBG and thyroid-binding globulin. Additionally, the risk for VTE and stroke appears lower with transdermal preparations. Transdermal estrogen can be found as a patch, gel, or spray (Table 3). Typically, therapy initiation starts with the lowest dose necessary to control the symptoms, and the dose can be incrementally increased until symptom resolution occurs. With gels and sprays, the harmful effects of the medication can be transferred to close contacts and pets that may touch the skin area where the gel or spray had been applied.

4.4 Vaginal Preparations and Rings

Local estrogens are preferable if the primary menopausal symptom is vaginal atrophy. Patients complaining of vaginal dryness, burning, pain or dyspareunia are likely to benefit from estrogen applied directly to the vaginal tissue. Vaginal estrogen provides women with genitourinary benefits of estrogen without the systemic exposure and risks of oral estrogen. While the majority of vaginal estrogens supply enough medication to treat atrophy, one preparation, Femring, has enough systemic absorption to treat vasomotor symptoms as well (Table 4).

Table 3 Transdermal estrogen products

Ingredient	Product name	Available dosage (mg of estradiol/day)
Patch		
17β-estradiol	Alora	0.025, 0.05, 0.075, 0.1 twice/week
	Climara	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 once/week
	Estraderm	0.05, 0.1 twice/week
	Menostar	0.014 once/week
	Minivelle	0.0375, 0.05, 0.075, 0.1 twice/week
	Vivelle-Dot	0.025, 0.0375, 0.05, 0.075, 0.1 twice/week
17β-estradiol/levonorgestrel	ClimeraPro	0.045/0.015 once/week
17β-estradiol/norethindrone acetate	Combi-patch	0.05/0.14, 0.05/0.25 twice/week
Gel		
17β-estradiol	Divigel	0.25, 0.5, 1.0
	EstroGel	0.75 up to 1.5
	Elestrin	0.52, 1.04
Spray		
17β-estradiol	Evamist	1.53 daily

Table 4 Vaginal estrogen products

Ingredient	Product name	Available dosage
Cream		
17β-estradiol	Estrace Vaginal Cream[a]	0.1 mg/g
Conjugated equine estrogen	Premarin Vaginal Cream[a]	0.625 mg/g
Ring		
17β-estradiol	Estring[a]	2 mg/90 days
Estradiol acetate	Femring[b]	0.05, 0.1 (mg/day over 90 days)
Tablet		
Estradiol	Vagifem[a]	10 mcg/tab

[a]Primary indication is for genitourinary atrophy
[b]Need progesterone if uterus intact

4.5 Conjugated Estrogen + Bazedoxifene

In 2013, the Food and Drug Administration (FDA) approved Duavee® (conjugated estrogen 0.45 mg and bazedoxifene 20 mg) for the treatment of vasomotor symptoms associated with menopause and for the prevention of osteoporosis in postmenopausal women with a uterus. The tablet is a daily oral preparation to control vasomotor symptoms. Bazedoxifene is a selective estrogen receptor modulator that has estrogen-like effects on the bone and lipids but antiestrogenic effects on the uterus and breast. Duavee has been shown to increase bone mineral density of the lumbar spine and hip when compared to placebo, but it is not recommended as first-line therapy for the treatment of osteoporosis (Lindsay et al. 2009). The most common side effects include muscle spasms, nausea, and diarrhea.

4.6 Selective Estrogen Receptor Modulators

In 2013, the FDA approved Osphena® (ospemifene) for the treatment of moderate to severe dyspareunia secondary to menopausal vulvar and vaginal atrophy. Ospemifene is a good

choice for women with dyspareunia and vaginal dryness who do not want to use vaginal preparations or cannot place vaginal products due to comorbid conditions like obesity or arthritis. One 60 mg tablet is ingested daily.

As an estrogen agonist/antagonist, ospemifene binds to estrogen receptors and activates estrogenic pathways in the vagina and blocks the estrogenic pathway in the breast and uterus. This medication can cause hot flashes and has not been studied in women with a history of breast cancer.

4.7 Bioidentical Hormones

A bioidentical hormone is a marketing term often used to describe custom-compounded HRT products. Many times, they are plant derived and are chemically or structurally similar to those hormones produced by the body. Custom compounds are made based on serum or saliva tests and combine a variety of hormones including estradiol, estrone, estriol, progesterone, testosterone, and dehydroepiandrosterone. Serum and salivary testing for the initiation or modification of hormone therapy has not been found to be useful and therefore is not recommended. Compounded bioidenticals are not recommended because there is limited quality control and evidence for their safety and efficacy is lacking.

5 Other Potential Benefits

Hormone replacement therapy may provide benefits other than relief of climacteric symptoms. This portion of the review will discuss the potential benefits of HRT on lower urinary tract symptoms, urinary tract infection, sexual function, and dermatologic aging.

5.1 Lower Urinary Tract Symptoms

Estrogen and progesterone receptors are expressed throughout the entire lower urinary tract (LUT), and estrogen receptors alone are seen in portions of the levator ani muscle which aid in LUT function. Estrogens may affect benefit by increasing urethral resistance and by raising the detrusor smooth muscle and nerve thresholds (Versi and Cardozo 1988). A meta-analysis of randomized and nonrandomized studies showed inconsistent improvement in stress incontinence symptoms with systemic estrogen therapy; therefor currently HRT is not recommended therapy for stress urinary incontinence (Ahmed Al-badr 2003). Systemic estrogen therapy use in the management of overactive bladder has shown promise in rat studies, yet these findings have not been confirmed in human randomized controlled trials and there is some evidence that systemic hormone replacement may make incontinence worse (Eriksen and Rasmussen 1992). Though systemic estrogen may not be of benefit for incontinence, there is evidence exhibiting local vaginal estrogen therapy resulted in improvement of frequency, urgency, and nocturia compared to placebo (Cordoza et al. 2001).

5.2 Urinary Tract Infection

Urinary tract infections in postmenopausal women commonly cause lower urinary tract symptoms including dysuria, frequency, and urgency. Estrogen therapy in the postmenopausal population modifies vaginal pH and reverses the microbiological changes in the vagina secondary to menopause. Evidence from meta-analysis suggests use of estrogen therapy, especially vaginal preparations, may decrease the risk of recurrent urinary tract infections and should be considered as a therapeutic option in postmenopausal women with recurrent infections (Cody et al. 2009).

5.3 Sexual Function

Maintenance of sexual function throughout a woman's life is of paramount importance. A study by Gonzalez et al. compared pre- and postmenopausal sexual function. Postmenopausal women report a global decrease in sexual function, but only significant dysfunction exist in the

lubrication and sexual pain domains (González et al. 2004). This study also compared the rates of sexual dysfunction between those patients utilizing HRT and those who are not and found that HRT improved orgasm, lubrication, and pain associated with intercourse. Women on HRT reported a higher level of sexual satisfaction compared to those who were not (González et al. 2004).

5.4 Dermatologic Aging

Many ask if hormone therapy can slow dermatologic aging. To answer this question, Sator et al. performed a randomized double-blind placebo controlled trial evaluating the effects of HRT on dermatologic metrics in postmenopausal women. Women in this study received 7, 28-day cycles of combined systemic HRT or placebo. The authors found a significant increase in skin elasticity, skin hydration, and skin thickness (Sator et al. 2007). This data suggests although dermatologic aging is not an indication for HRT, improvements in skin metrics may be a beneficial side effect in those utilizing HRT for another indication (Sator et al. 2007).

6 Special Populations

While hormone replacement therapy can provide relief of climacteric symptoms for many women, there are certain populations who require special consideration prior to implementing any hormonal regimen. An understanding of the risk-benefit ratio of utilizing hormone replacement therapy in these populations allows practitioners to counsel their patients regarding the appropriateness of hormone replacement therapy in patients with complex medical histories.

6.1 Endometrial Cancer

It is common knowledge that estrogen has a stimulating effect on endometrial tissue. The Society for Gynecologic Oncology's Clinical Practice Committee reviewed the literature regarding the relationship between HRT and endometrial carcinoma. The studies reviewed assessed the risk of endometrial carcinoma in women with no previous history of endometrial carcinoma and showed an elevated risk in women using long cycle HRT for greater than 5 years and women on long cycle or sequential cycle HRT for greater than 10 years. Patients using tibolone showed no increased risk for endometrial carcinoma. Observational studies show unopposed estrogen is associated with a two- to threefold increased risk in endometrial carcinoma but that this risk was mitigated to baseline with the addition of a progestational component (Burke et al. 2014). Shim et al. performed a meta-analysis of one randomized controlled trial and five observational studies totaling over 1000 patients to assess the effects of HRT on the recurrence of endometrial cancer. The results of this analysis demonstrated no increased risk of recurrence between users of HRT and controls. A subgroup analysis of cancer stage and type of HRT provided confirmed the overall study results exhibiting no increased recurrence risk by these strata (Shim et al. 2014). In those patients with estrogen and progesterone receptor negative carcinomas, it seems a reasonable approach to consider immediate implementation of HRT. In those patients with high risk tumors, estrogen and progesterone receptor positive, consideration may be given for hormone replacement therapy, but implementation should be delayed at least 5 years post diagnosis as the recurrence risk is highest in the first 5 years following diagnosis. Due to the protective nature of progestational component of HRT, combination therapy is recommended if HRT is to be initiated in this population (Rossouw et al. 2002).

6.2 Breast Cancer

Many breast cancers are hormone-sensitive tumors, and the aversion to HRT in this population is reasonable. The question remains: Should all women with a personal history of breast cancer be excluded from HRT? There are women in this cohort that experience severe climacteric

symptoms who would consider HRT to improve their quality of life; therefore a thorough discussion of the risk-benefit ratio in this population is paramount.

As shown in the WHI of postmenopausal women, the use of combined HRT resulted in a 26 % greater relative risk of breast cancer compared to those who were not exposed to HRT. Interestingly, those exposed to estrogen alone had no increased risk of breast cancer highlighting that the association is unclear (Rossouw et al. 2002).

Progestins alone are the best studied agents for the treatment of climacteric symptoms following breast cancer and have shown promise in controlling vasomotor symptoms. The risk of breast cancer recurrence with the use of progestins has not yet been established and may potentially increase risk of breast cancer recurrence (Rossouw et al. 2002). Currently, the use of progestin therapy, although effective in treating vasomotor symptoms, has not been proven a safe alternative for women with a history of breast cancer (Hickey et al. 2005).

Similar to estrogen and progesterone therapies, tibolone has shown improvement in climacteric symptoms, but a large randomized controlled trial evaluated the recurrence risk of breast cancer with the use of tibolone HRT and showed an increased risk of recurrence in the tibolone group with a hazard ratio of 1.40 (Kenemans et al. 2009). Currently, use of tibolone therapy in women with a history of breast cancer is not recommended.

The use of hormone replacement therapy as first-line management in women with a history of breast cancer is not recommended, but in those informed patients with severe vasomotor symptoms and in those patients with metastatic breast cancer where quality of life is of primary concern, hormone replacement therapy may be considered (Fritz and Speroff 2011).

6.3 Uterine Leiomyomas

Although estrogen and progesterone stimulate the growth of uterine myoma, in postmenopausal women on HRT this phenomenon is not seen. It is important to remember when counseling patients that the dose of estrogen and progesterone supplied in hormone replacement therapy is well below the endogenous premenopausal hormone level and the hormone doses provided in oral contraceptive pills. Multiple studies have confirmed that the use of standard doses of estrogen, progesterone, or tibolone results in no changes in uterine or myoma volumes on pelvic ultrasound (Ahmed Al-Badr 2003).

6.4 Liver Disease

Chronic liver disease often precipitates osteoporosis, and when combined with menopause, the risk of osteoporosis is amplified. The use of HRT as a method of osteoporosis prevention is preferred, but do hormones increase the risk of liver disease exacerbation? A study evaluating the effect of transdermal estradiol and norethisterone on serum liver enzymes in patients with Chronic Hepatitis B and C showed no difference between those on HRT or placebo (Rinaldi et al. 2005). Another study of postmenopausal women with primary biliary cirrhosis who were treated with estrogen replacement therapy for osteoporosis produced similar results showing no progression of disease with HRT versus age-matched controls (Menon et al. 2003). Based on the results of these studies, HRT appears safe in women with liver disease. If HRT is initiated in this population, baseline liver enzymes should be obtained every 6 months to ensure the disease process is stable (Fritz and Speroff 2011).

7 Conclusion

With the aging population, management of climacteric symptoms will become routine in gynecologic practice. A thorough understanding of the risks and benefits of hormonal therapy will position providers to provide superior counseling regarding the appropriateness of managing climacteric symptoms via a hormonal approach.

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Management of Vaginal and Vulvar Lesions in the Older Woman

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Abstract

Vaginal and vulvar lesions in the elderly patient can be caused by a variety of disorders from benign dermatoses to malignancies. Physiologic changes of aging and menopause produce conditions and symptoms that can make diagnosis challenging. With a few exceptions, new lesions of the vagina or vulva warrant biopsy to obtain an accurate diagnosis. Histological diagnosis will almost always provide guidance for initial management.

Keywords

Genital ulcer • Genital lesion • Vaginal • Vulva • Dermatoses • Postmenopausal

1 Introduction

Postmenopausal women may present with a variety of gynecologic concerns regarding lesions of the vaginal-vulvar region. Physiologic changes of menopause and aging alone can prompt these patients to seek medical care, and providers in multiple fields including gynecology, primary care, and dermatology may provide the initial evaluation of these lesions.

The differential diagnosis is broad when evaluating patients with a lesion of the vagina or vulva and includes both benign and malignant conditions. Although some lesions will have characteristics to suggest a particular diagnosis, the mainstay for diagnosis of vulvar and vaginal

Table 1 Differential diagnosis of vulva and vaginal lesions

Diagnosis	Initial treatment
Infectious	
Primary or secondary herpes simplex virus	Acyclovir, valacyclovir (oral)
Vulvovaginal candidiasis	Antifungal (oral or topical)
Systemic disorders	
Crohn's disease	Mild to mid-potency topical steroid
Sarcoidosis	Mild to mid-potency topical steroid
Vulvar dermatosis	
Lichen sclerosus	High-potency topical steroid (clobetasol)
Lichen planus	High-potency topical steroid, calcineurin inhibitors
Lichen simplex chronicus	Mild to mid-potency topical steroid
Vulvovaginal atrophy	Topical estrogens
Premalignant and malignant conditions	
Vulvar or vaginal intraepithelial neoplasia	Wide local excision
Vulvar squamous carcinoma	Referral to gynecology oncology (vulvectomy)
Vulvar or vaginal melanoma	Referral to gynecology oncology, dermatology
Paget disease	Referral to gynecology oncology (vulvectomy)

lesions is tissue biopsy and evaluation by a trained pathologist. The management of these lesions is guided by the tissue diagnosis.

1.1 Presentation

Most women may initially present with pruritus and/or irritation in the vulvovaginal region and have a subsequently noticed lesion on exam; pain may be associated with the lesion. Others may present with dyspareunia. These symptoms may be transient in nature or more long-standing. Onset is usually gradual but may also be acute.

2 Initial Assessment: History and Physical Exam

The primary focus of the initial assessment of a vaginal or vulvar lesion in the postmenopausal age group is to ensure the lesion is not a malignancy. A thorough history and physical exam must be performed, as well as a biopsy of the affected region.

Key points of the history include duration and quality of symptoms and associated lesion, prior history of genital lesions, use of topical ointments, creams, washes to the region, new sexual partner, urinary incontinence, lesions in other regions (oral mucosa), and any precipitating factors (including trauma). All medical comorbidities should be noted. Physical exam should be focused on assessing the genital region including assessing the labia majora and minora and the entire vagina to evaluate location and size of lesion, painful or nonpainful, thinning or scarring of tissue, and any associated discharge. Additionally, as part of the examination, an assessment of other mucosal surfaces (oral mucosa) for lesions is warranted.

The most common cause of vulvovaginal discomfort is atrophy. The lack of circulating estrogen in the postmenopausal state causes atrophy of the vaginal and vulvar tissue and leads to itching, burning, and irritation. This is easily treated with the aid of lubricants and topical estrogen therapy. There is usually no associated discrete lesion (see Table 1 for differential diagnosis).

The prevalence of urinary incontinence increases with advancing age of the patient and can also lead to irritation and breakdown of the tissue resembling an ulcer. Control of the incontinence will improve these symptoms.

3 Biopsy

The mainstay of diagnosis is to biopsy the area of concern. The most simple and common way to perform a biopsy of vulvar lesions is through a

punch biopsy. To obtain such a sample, the skin and subcutaneous tissue should be injected with a local anesthetic such as 1 % lidocaine with epinephrine after prepping the skin with antiseptic. A 3- or 4-mm Keyes punch biopsy is used to obtain a tissue specimen by applying pressure in a rotating fashion; the skin is then elevated with forceps and the base is excised with scissors to obtain a small piece of the skin and subcutaneous tissue. Silver nitrate or an interrupted absorbable suture can be used for hemostasis and reapproximation of the tissue.

Biopsy of a vaginal lesion requires examination with a speculum and specialized biopsy instruments. Kevorkian biopsy forceps or Tischler biopsy forceps will obtain sufficient tissue in most situations. One 1 % lidocaine can be used for a local anesthetic; however, for small biopsies of lesions in the upper vagina, anesthetic is not routinely needed. Silver nitrate is used for hemostasis.

The final histologic diagnosis will help categorize the vulvovaginal lesion and guide the management strategies. The following conditions are some of the most frequent causes of vaginal or vulvar lesions in the elderly patient (Table 1). The presentation and initial management of each condition is discussed below.

4 The Vulvar Dermatoses

4.1 Vulvovaginal Atrophy

Vulvovaginal atrophy results from decrease in circulating estrogens as part of the normal aging process and has been a reported complaint in up to 47 % of postmenopausal women. This is a gradual process where there is a thinning of the superficial epithelial cells of the vagina and vulva leading to decreased elasticity and subsequent narrowing and shortening of the vagina. Most commonly, women present with vaginal dryness and irritation leading to dyspareunia; nonsexually active women may experience no symptoms or vaginal dryness.

Biopsy is not necessary for diagnosis if there are no discrete lesions. Nonhormonal treatment can be started initially with lubricant and petroleum jelly. If there is no improvement, then topical estrogens are typically utilized. There are several options ranging from estrogen-based creams and tablets used 2–3 times per week as well as an estrogen-containing vaginal ring replaced every 3 months by patient. There are several relative contraindications to topical estrogen use including undiagnosed vaginal bleeding and personal history of breast cancer (Table 2). Vaginal dilators can be used in conjunction with topical therapy if there has been any narrowing of the vagina. Biopsy should be considered in any women refractory to estrogen treatment or if a localized lesion or skin discoloration exists.

4.2 Lichen Simplex Chronicus

Lichen simplex chronicus is a condition of the skin that results from repetitive itching and scratching cycles. In its early stages, it will present as an erythematous plaque and then progress to thickening and scaling of the area as results of scratching. It is important that clinicians remember that lichen simplex chronicus is not a primary lesion but rather a secondary lesion as a result of chronic scratching – pruritic cycles. The underlying cause for the pruritic symptom is not always known, but common causes in the elderly patient including hypoestrogenic atrophy, irritation from urine secondary to urinary incontinence, and candidiasis should be evaluated and treated.

Patients should be asked regarding any changes to hygiene products or clothing that may lead to a contact dermatitis and subsequent pruritus. Conditions such as depression and anxiety can contribute to a psychological component of itching and if present should be appropriately treated.

Because the driving factor for lichen simplex chronicus is pruritus, treatment should entail therapy to relieve the pruritic symptoms and allow the lesion to heal as well as establish and manage the primary cause of the pruritic-scratching cycles. High-potency corticosteroids such as clobetasol 0.05 % can be used for initial therapy or, for milder cases, a medium-potency steroid such as

mometasone 0.1 %. Additional measures to consider include using antihistamines at night to relieve the pruritus and using sitz baths during acute pruritic episodes when the patient has the urge to itch. Petroleum jelly can also be used liberally. Loose nonconstrictive clothing and cotton underwear are also recommended. Breaking the pruritic-scratching cycles is essential to long-term management.

4.3 Lichen Sclerosus

Lichen sclerosus is a chronic inflammatory disorder of the genital skin that is commonly found on the vulva. It can occur at any age but is most often seen in postmenopausal women presenting as a symptomatic lesion with itching. It can also be discovered incidentally on exam. Due to its potential association with malignancy, providers should have a low threshold to biopsy suspected lichen sclerosus at the time of initial diagnosis or when lesions do not respond as expected to treatment. The mainstay of treatment is high-potency topical corticosteroids; most commonly 0.05 % topical clobetasol used twice daily for up to 16 weeks with initial diagnosis which will lead to significant improvement for most patients.

Following resolution of symptoms and improvement of lesion appearance, patients can begin to taper application; one common protocol would be to apply the ointment once daily for a month and then twice weekly for 3 months. It is important that patients be educated about the chronic nature of this condition. Their condition will likely require episodic treatment. A lower potency steroid such as triamcinolone can be used for more regular application and liberal use of petroleum jelly with a high-potency steroid used for flare ups. Additionally, topical estrogen can be used in conjunction with the steroids to treat the concomitant vaginal atrophy.

Patients being treated chronically with topical corticosteroids for lichen sclerosus should have regular evaluation with the managing provider. Any lesions that do not respond to potent topical corticosteroids should be reappraised and potentially biopsied. Additionally, chronic use of these medications can lead to atrophy, fungal infections, and striae formation and may require alteration of the treatment regimen or discontinuation. Patient compliance with a prescribed regimen is an important factor in long-term improvement.

It should be noted that occasionally women with lichen sclerosus can present with distortion of labia leading to labial fusion as well as vaginal canal obliteration. This can lead to inability to have intercourse and in more severe cases obstruction of the urethra. Surgical excision of scarred tissue with the use of vaginal dilators in conjunction with high-potency topical steroids is required to treat these sequelae of lichen sclerosus.

Rarely, lichen sclerosus can be complicated by squamous cell carcinoma. The incidence of this is reported to be between 0.3 and 4.9 % (Fistarol and Itin 2013). Any suspicious lesion or skin discoloration should be biopsied. It is unclear if treatment of lichen sclerosus can prevent progression to a malignant condition; however, treatment does prevent genital scarring and obliteration of the vaginal canal as discussed above.

4.4 Lichen Planus

Lichen planus is a condition whose etiology is unknown but is suspected to be autoimmune in nature. It leads to lesions, which can be found on the genitals, the oral mucosa, or the scalp. There are several subtypes of this condition, and the lesions can have varied characteristics from erosive and erythematous lesions to papular or hypertrophic lesions.

Patients with lichen planus will most commonly present with acute onset symptomatic lesions. These lesions will typically be found on the oral mucosa, flexor surfaces of the extremities, and in the genital region. The less common is cutaneous involvement of the scalp or fingernails. At least half of women who are found to have oral lesions will also have genital lesions (Di Fede et al. 2006). Though the vulva is the more likely genital site of lesions, vaginal involvement can occur as well. Lichen planus can be diagnosed clinically if lesions are classic in their appearance

and location; however, punch biopsy is warranted for any atypical lesion or any lesion unresponsive to therapy.

Initial treatment of vulvar lichen planus involves topical corticosteroids. A high-potency steroid cream such as 0.05 % clobetasol can be used daily for 4–8 weeks until improvement of the lesions and symptoms. The condition is chronic and likely to recur, and so prolonged and possibly indefinite maintenance therapy is usually needed. After initial treatment with a high-potency steroid, the treatment can be tapered by either decreasing the frequency of dosing or switching to a less potent steroid such as triamcinolone ointment. Patients should continue this therapy until resolution of the lesions or acceptable remission while undergoing periodic evaluations every 3–6 months to evaluate for tissue atrophy, which is the most common side effect of topical steroid use.

The majority of patients with lichen planus treated with an appropriate corticosteroid regimen will see resolution or improvement in their lesions. For patients refractory to treatment with corticosteroids, topical calcineurin inhibitors such as tacrolimus 0.1 % or pimecrolimus 1 % can be used. Second-line agents include topical tacrolimus in either the 0.03 % or 0.1 % formulation. The cost of this medication limits its use as a first-line agent but can be considered in addition to or following unsuccessful treatment with corticosteroids.

4.5 Psoriasis

Psoriasis is a chronic skin condition that classically presents as erythematous plaques with a silver scaling. Although it is a common skin condition, it usually presents in adolescence or young adulthood rather than as a new lesion in an elderly patient. When psoriasis affects the genital area in women, it is more likely to be found on the hair-bearing vulvar regions than in the mucous membranes. In a patient with a history of psoriasis presenting with a vulvar lesion whose findings are characteristic of psoriasis, biopsy is not immediately indicated.

Initial treatment should include topical corticosteroids such as 0.05 % clobetasol daily, which can be tapered to less frequent administration or to a lower potency steroid. For genital lesions that are refractory to corticosteroids, a biopsy should be obtained to confirm diagnosis. Alternatives for treatment include topical calcitriol ointment administered twice daily for refractory lesions.

5 Premalignant and Malignant Lesions

5.1 Vulvar Intraepithelial Neoplasia (VIN)

Vulvar intraepithelial neoplasia (VIN) is a dysplastic, premalignant condition of the vulva. In the past, these lesions were classified into three grades (VIN I–III). However, since 2004 low-grade squamous lesions are no longer termed VIN because these likely represent a transient HPV infection (Committee on Gynecologic Practice of American College Obstetricians and Gynecologists 2011). For high-grade lesions, a two-part classification system is now used where lesions are classified as usual-type VIN or differentiated VIN. The usual-type VIN is associated with HPV infection, whereas the differentiated type is more likely to arise in the setting of conditions such as lichen sclerosis. The differentiated type is more likely to be associated with squamous cell carcinoma than the usual type (Sideri et al. 2005).

The majority of women with VIN will present with vulvar pain or itching (van Seters et al. 2005). However, it is not uncommon for these lesions to be discovered incidentally on exam. In older patients with risk factors including known HPV infection, smoking, or immunodeficiency, providers should have a high index of suspicion for VIN. These lesions are usually multifocal and can be elevated, ulcerated, and atypically colored (van Seters et al. 2005). Biopsy of any visible lesion is warranted to provide diagnosis. If a patient's history and symptoms raise suspicion for VIN without a visible lesion, a trained colposcopist should evaluate the vulva for lesions. If a biopsy is performed without colposcopy and is determined to be VIN,

colposcopy should be considered to evaluate for further lesions.

For most patients, surgical excision of VIN is the treatment of choice. However, there are circumstances where medical therapy or ablative treatment with a laser is warranted. In patients with usual-type VIN and no concern for malignancy based on the lesion characteristics and the patient's history, ablation of the lesion with laser or off-label treatment with topical therapy using 5 % imiquimod may help preserve the genital anatomy while providing effective treatment (Terlou et al. 2011). Inflammatory side effects with topical treatment are common and patients should be treated with a 16-week course of therapy.

Surgical excision is an acceptable treatment for any VIN lesion in an appropriate surgical candidate. Wide local excision is the preferred procedure. Ideally, 5–10 mm of clear margin is obtained with excision. Clear margins following excision decrease the likelihood of recurrence but do not prevent it completely (Committee on Gynecologic Practice of American College Obstetricians and Gynecologists 2011).

Independent of treatment modality, 30–50 % of patients with VIN will have recurrent lesions. Patient should be counseled on smoking cessation if needed and followed every 6 months with an exam and colposcopy.

5.2 Vulvar Carcinoma

Squamous cell carcinoma of the vulva is the most common histological subtype of vulvar cancer. It is commonly an HPV-related process, and its incidence increases with increasing age of the patient. Vulvar carcinoma may appear as a raised, ulcerated, or discolored lesion. Symptoms such as itching may be present and less commonly patients may have bleeding. The patients will often report symptoms lasting for months to years before diagnosis (Jones and Joura 1999). Diagnosis is made by biopsy. If multiple lesions are present and there is high suspicion for malignancy, multiple biopsies can be performed to ensure accurate diagnosis. In patients with a history of vulvar dysplasia, vulvoscopy can be performed to guide biopsy of the most concerning lesions. As with other gynecologic malignancies, patients with histologically proven vulvar cancer should be referred to a specialist in gynecologic oncology.

5.3 Vulvovaginal Melanoma

Melanoma of the vulva or vagina is a rare condition encompassing far less than 1 % of all melanomas (Chang et al. 1998). These lesions are more often found on the vulva than on the vagina. Presentation can be varied and may include symptoms of itching, bleeding, discharge, or a visible mass. Melanoma of the genital region will usually have a similar appearance as cutaneous melanomas with characteristic larger size, asymmetry, irregular borders, and variations of dark colors. These lesions can sometimes be amelanotic with a little to no discernable pigment making them more likely to be missed on examination. Diagnosis is of course made by tissue biopsy, and an excisional biopsy is generally considered the standard of care. A diagnosis of vulvovaginal melanoma warrants a referral to a gynecologic oncologist for appropriate staging and care (Pflugfelder et al. 2010). As a whole, these malignancies have a poor prognosis even compared to cutaneous lesions which is likely due in part to a delayed diagnosis given their location.

5.4 Vaginal Carcinoma

Squamous cell carcinoma of the vagina is rare but is the most common malignancy of primary vaginal origin with a peak of incidence in women aged 60–80. The majority of these cancers are associated with HPV, and having a history of cervical dysplasia is a risk factor for vaginal cancer (Smith et al. 2009). Patients with vaginal carcinoma will most often present with painless bleeding but can also present with pain or urinary symptoms in more advanced disease (Creasman 2005). Diagnosis of vaginal carcinoma is made by biopsy. Patients with a diagnosis of vaginal carcinoma should be referred to a gynecologic oncologist for specialized management.

5.5 Paget Disease

Extramammary Paget disease is a rare condition but is more common in women than in men and incidence increases with increasing age. Patients typically present with itching and will usually report a long and less acute onset of their symptoms. The lesions will usually be an erythematous plaque with some whitened epithelium and can often appear clinically similar to the vulvar dermatoses including psoriasis or lichen simplex chronicus. This diagnosis is often made after an incorrectly diagnosed lesion fails to respond to initial treatment with corticosteroids. Diagnosis is made by tissue biopsy. Although extramammary Paget disease is less often associated with an underlying malignancy than Paget disease of the breast, any patient with this diagnosis should undergo a work-up for a gastrointestinal or genitourinary malignancy (Feuer et al. 1990).

6 Conclusion

Providers should have a low threshold to biopsy any new genital lesion in the elderly patient. Patient's with a history of cervical dysplasia and risk factors such smoking and HPV infection should raise concern for the possibility of a malignancy when presenting with vaginal or vulvar lesions. Additionally, other less common etiologies in this age group should be considered such as infectious causes including a primary or secondary herpes simplex virus infection, vulvovaginal candidiasis, or ulcers secondary to systemic disorders such as inflammatory bowel disease (Crohn's disease). In the absence of histological diagnosis, any lesion that does not respond to initial therapy should also be rebiopsied to exclude malignancy.

7 Cross-References

- ▶ Benign Vulvar and Vaginal Pathology
- ▶ Diagnosis and Management of Vulvar Cancer
- ▶ Diagnosis and Management of Vulvovaginitis
- ▶ Malignant Vulvar and Vaginal Pathology
- ▶ Management of Intraepithelial Lesions of the Cervix
- ▶ Management of Pelvic Pain in the Older Woman
- ▶ Management of Pelvic Pain, Dyspareunia, and Endometriosis
- ▶ Management of Vulvodynia

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Management of Ovarian Masses in the Older Woman

Alexander Melamed and Devin T. Miller

Contents

Abstract

Ovarian masses are frequently encountered among older women. While postmenopausal women are at elevated risk of ovarian cancer, even among this population most adnexal masses (ovarian and extra-ovarian) are benign. The evaluation of an adnexal mass seeks to identify patients with malignancy, especially ovarian cancer, who require surgical management while avoiding unnecessary surgery among women with benign conditions. Pelvic ultrasound is the first-line imaging study for characterizing an ovarian mass and usually the only necessary imaging modality. When ultrasound is equivocal, magnetic resonance imaging may further characterize an adnexal mass. Despite frequent use, serum tumor markers are of limited use in differentiating benign from malignant masses. Among women triaged to surgery based on clinical impression and radiologic findings, serum tumor markers may aid in determining which patients should be referred to a gynecologic oncologist. Patients with masses who are at very high risk of ovarian cancer should be referred to a gynecologic oncologist for further management.

Keywords

Ovarian mass • Adnexal mass • Ovarian neoplasms

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1 Introduction

Ovarian masses in women over 50 years of age are a common clinical problem. Frequently such masses are encountered incidentally and may represent benign, borderline, or malignant neoplasms of the female reproductive tract, metastasis from distant organs, or a variety of nonneoplastic processes (Table 1). Since older women are at elevated risk of malignant neoplasms, the evaluation of ovarian masses in this population attempts to differentiate ovarian cancer, which requires prompt surgical intervention, from benign lesions that can often be managed conservatively. This chapter will review the epidemiology, clinical presentation, evaluation, and management of the adnexal mass (ovarian and extra-ovarian) among older women, with focus on postmenopausal women.

2 Epidemiology

In the United States, ovarian cancer is the fifth most common cause of cancer-related mortality among women and the most lethal gynecologic malignancy. Annually, over 21,000 American women are diagnosed with ovarian cancer and more than 14,000 succumb to the disease. The lifetime risk of developing ovarian cancer is approximately 1 in 70. The prognosis of ovarian cancer is related to the degree of spread. While the 5-year survival of women with ovarian cancer that is isolated to the ovaries exceeds 90 %, a majority of patients are diagnosed with metastatic disease, for which the 5-year survival rate is 27 %.

Age is an important risk factor for ovarian cancer, with incidence increasing steeply in the postmenopausal period (Fig. 1). Hereditary cancer syndromes including BRCA1 and BRCA2 mutation and hereditary nonpolyposis colorectal cancer syndrome (i.e., Lynch syndrome) predispose women to many types of malignancies, including ovarian cancer. However, the vast majority of malignant ovarian neoplasms arise sporadically. Additional risk factors for ovarian cancer include nulliparity, infertility, and endometriosis. Long-term oral contraceptive use, tubal ligation, salpingectomy, and hysterectomy are protective for ovarian cancer.

Adnexal masses are far more common than ovarian malignancies. Consequently, most ovarian masses, even in postmenopausal women, are benign. In large screening studies of asymptomatic postmenopausal women in the United States, 14–17 % of women have evidence of ovarian enlargement, cysts, or solid masses on transvaginal ultrasound. Autopsy studies of women who died of non-gynecologic causes have confirmed this prevalence of benign ovarian lesions.

It is difficult to estimate the true frequency of benign and malignant causes of ovarian masses because women who are asymptomatic, and have

Table 1 Differential diagnosis of adnexal mass

Nonneoplastic lesions	Benign neoplasms	Malignant neoplasms
Ovarian	Ovarian	Ovarian
Follicular cyst	Cystadenoma (serous or mucinous)	Epithelial carcinoma
Functional cyst	Cystadenofibroma	Germ cell carcinoma
Ectopic pregnancy	Benign cystic teratoma	Sex-cord stromal tumors
Endometrioma	Fibroma	Malignant Brenner tumor
Tubo-ovarian abscess	Benign Brenner tumor	Extra-ovarian
Extra-ovarian	Extra-ovarian	Fallopian tube carcinoma
Para-tubal cyst	Uterine leiomyoma	Appendiceal carcinoma
Hydrosalpinx or pyosalpinx	Broad ligament leiomyoma	Retroperitoneal sarcoma
Pelvic abscess	Cystic lymphangioma	
Ectopic pregnancy	Hemangioma	
Peritoneal inclusion cyst		
Appendiceal mucocele		
Bladder or ureteral diverticulum		
Vascular or lymphatic lesions		

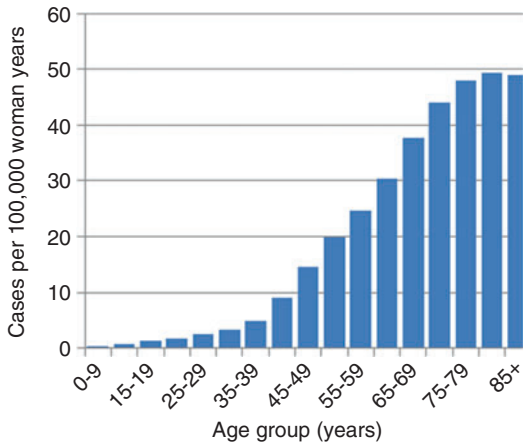

Fig. 1 Age-specific incidence of ovarian cancer (Source: National Cancer Institute, Surveillance, Epidemiology, and End Result program (SEER))

benign radiologic findings, are often managed expectantly. For this reason, surgical case series necessarily overestimate the actual incidence of malignant lesions. Among postmenopausal women who undergo surgery for a suspicious mass, the reported frequency of cancer ranges from 36 % to 59 %.

3 Clinical Presentation

Most women diagnosed with an ovarian mass are asymptomatic and are found to have an adnexal lesion during the course of imaging obtained for an unrelated indication. However, some women may develop pain or pressure symptoms. Ovarian torsion should be considered in women who present with severe, acute onset, pelvic pain, and an ovarian mass, especially in the presence of nausea and vomiting. Ovarian torsion may involve benign or malignant masses. In women who are still menstruating, pain associated with an ovarian mass may represent a ruptured hemorrhagic cyst or ectopic pregnancy. Women with a tubo-ovarian abscess may present with an adnexal mass in association with pain and fever. After menopause, tubo-ovarian abscesses are rare and frequently associated with a concomitant gynecologic malignancy.

Most women who are diagnosed with epithelial ovarian cancer, even with early-stage disease, experience nonspecific symptoms prior to diagnosis including: abdominopelvic discomfort or pain, swelling or bloating, increasing abdominal size, urinary symptoms, or change to bowel habits (American College of Obstetricians and Gynecologist, 2011). While such symptoms may be attributed to many conditions, there is evidence that women who will ultimately be diagnosed with ovarian cancer more often have daily symptoms and symptoms that are more severe than those experienced by women who do not develop cancer. In women with an ovarian mass, postmenopausal bleeding or virtualization may suggest the presence of a steroid-secreting sex-cord stromal tumor. Women with an extrapelvic malignancy and bilateral solid ovarian masses may have ovarian metastasis.

4 Differential Diagnosis

The differential diagnosis of an adnexal mass is extensive and includes many ovarian and extra-ovarian processes (Table 1). It is not always possible to distinguish the origin of an adnexal mass, especially when it is large.

4.1 Cystic Masses

Unilocular cystic masses of the adnexa, which have no solid areas or septations and are smaller than 10 cm, are nearly always benign (Greenlee et al. 2010). In menstrual women, such lesions are usually follicular cysts. After menopause, a unilocular cyst is most frequently an ovarian cystadenoma, para-tubal cyst, or endometrioma. Other entities which may present as a unilocular adnexal cyst include bladder or ureteral diverticula, peritoneal inclusion cysts, and cystic lesions of gastrointestinal origin.

Cystic adnexal lesions with complex features including wall thickening, septations, or solid components may represent a variety of benign or malignant processes. Even in postmenopausal women, the majority of complex cystic adnexal

masses are benign, and most will resolve spontaneously. A corpus luteum is the most common cause of a complex cystic ovarian lesion in menstrual women. Among menopausal women, benign causes of complex adnexal cysts include ovarian cystadenomas (serous and mucinous), cystadenofibromas, endometriomas, mature cystic teratomas (dermoids), hemorrhagic ovarian cysts, tubo-ovarian abscesses, pelvic abscesses from diverticulitis or appendicitis, peritoneal inclusion cysts, appendiceal mucoceles, and lymphatic lesions. Complex cystic adnexal lesions may represent epithelial cancers of the ovary and fallopian tube. Solid components (referred to as papillary projections, excrescences, or nodules) within a cystic ovarian mass raise suspicion for malignancy, though most masses with solid components are benign.

4.2 Solid Masses

Completely solid adnexal lesions are frequently benign neoplasms, but may represent malignant disease. The most frequent causes of solid adnexal lesions are ovarian fibromas and pedunculated uterine leiomyoma. Fibromas occasionally occur in conjunction with ascites and a pleural effusion mimicking advanced ovarian malignancy (Meigs' syndrome). Other benign solid ovarian tumors include fibrothecomas, benign thecomas, and benign Brenner tumors. Malignant sex-cord stromal, Brenner, and germ cell tumors are usually solid ovarian lesions, though germ cell tumors are quite rare in older women. Ovarian metastases, which are most frequently from primary gastrointestinal, breast, or hematologic malignancies, are often solid bilateral lesions and represent 5–10 % of all ovarian malignancies.

5 Evaluation

5.1 History

A detailed history is essential in evaluating an older woman with an ovarian mass. The history should focus on assessing for risk factors, with a special emphasis on family history. A family history of early-onset breast cancer, or any ovarian cancer, should raise concern for a possibility of a familial tumor syndrome. A detailed assessment of abdominopelvic symptoms should be conducted, as most ovarian cancers are thought to produce nonspecific but persistent symptoms.

5.2 Physical Examination

Physical examination of an older patient with an adnexal mass may detect signs of advance malignancy. In advance ovarian cancer, abdominal examination may reveal evidence of ascites or omental caking, or, rarely, a Sister Mary Joseph node (umbilical metastasis). Inguinal or supraclavicular lymphadenopathy is occasionally present at the time of diagnosis. Pelvic examination (including rectovaginal exam) may reveal a large, fixed, or nodular pelvic mass or nodularity in the posterior cul-de-sac. However, physical examination has poor sensitivity (40 %) and specificity (90 %) for the detection of an adnexal mass and is unlikely to be useful in distinguishing between a benign and malignant mass in the absence of metastatic disease (Agency for Healthcare Research and Quality. 2006).

5.3 Serum Tumor Markers

Serum tumor markers have a limited role in the evaluation of older women with ovarian masses. Because adnexal masses are common, and ovarian cancer is rare, a biomarker must achieve extraordinary high sensitivity and specificity to reliably distinguish women with benign tumors from those with early ovarian cancer. While several serum markers are used in evaluating older women with adnexal masses, biomarkers alone cannot determine which masses require surgical management. On the other hand, when clinical and radiologic factors are used to determine that surgery is indicated, biomarkers may be useful in selecting high-risk patients for referral to a gynecologic oncologist.

5.3.1 Cancer Antigen 125 (CA 125)

The most frequently utilized, and best studied, serum tumor marker for the evaluation of an ovarian mass is CA 125. This transmembrane glycoprotein is expressed by coelomic and müllerian epithelia. Serum CA 125 is elevated in 80 % of women with ovarian, fallopian tube, and peritoneal carcinoma at the time of diagnosis. The utility of CA 125 in differentiating benign and malignant tumors is hampered by its low sensitivity in early-stage and non-serous histology. Additionally, many benign gynecologic conditions including ovulation, endometriosis, infection, pregnancy, fibroids, and other benign tumors have been associated with elevated CA 125, resulting in decreased specificity, particularly among women of reproductive age.

The utility of CA 125 for triaging patients with an adnexal mass to surgical or conservative management is highest among older women. In the postmenopausal patient with an adnexal mass, the sensitivity of a CA 125 greater than 35 U/mL for detecting ovarian carcinoma is 69–87 %, with a specificity of 81–93 % (Agency for Healthcare Research and Quality, 2006). The negative predictive value in this setting is only 72–87 %, meaning 13–28 % of postmenopausal women with an adnexal mass will have early ovarian cancer even when their CA 125 is normal. Therefore, an older woman with an ovarian mass and normal serum CA 125 may still require surgical management in the presence of symptoms, risk factors, family history, or radiologic features that raise concern for malignancy. Conversely, a postmenopausal woman with a suspicious mass and elevated CA 125 should be referred to a gynecologic oncologist for further evaluation (Table 2).

Table 2 Guidelines for referral of a woman with a pelvic mass to gynecologic oncologist

Premenopausal
Elevated CA 125 (greater than 200 U/mL)
Ascites
Evidence of abdominal or distant metastasis
History of ovarian or breast cancer in a first-degree relative
Postmenopausal
Elevated CA 125 (greater than 35 U/mL)
Ascites
Nodular or fixed mass
Evidence of abdominal or distant metastasis
History of ovarian or breast cancer in a first-degree relative

Guidelines American College of Gynecologic and Society for Gynecologic Oncology (2007)

An area of current investigation is the use of serial CA 125 measurements to improve detection of early-stage ovarian carcinoma. A rising CA 125, even in the normal range, may reflect growth of an occult ovarian cancer, whereas a stably elevated CA 125 may represent a begin process. Serial CA 125 measurement and the risk of ovarian cancer algorithm (ROCA) have been implemented in several large screening studies with promising results (Skates et al. 2003 and Menon et al. 2015). However, the utility of this approach in the context of a known adnexal mass has yet to be assessed.

5.3.2 Human Epididymis Protein 4 (HE4)

Human epididymis protein is a glycoprotein expressed by malignant müllerian epithelium. This biomarker is variably expressed according to histological subtype of epithelial ovarian carcinoma. In an immunostaining study, HE4 was expressed in 100 % of endometrioid tumors, 93 % of serous tumors, and 50 % of clear cell tumors, but not in mucinous tumors. Since its emergence, many studies have compared the performance of HE4 with CA 125. Results from these studies have varied, in part because of different thresholds and techniques for measuring HE4. Some studies have suggested that HE4 is more sensitive and specific than CA 125, while others have shown similar test characteristics.

5.3.3 Other Markers

Sex-cord stromal tumors and germ cell tumors may secret a verity of substances including alpha-fetoprotein, human chorionic gonadotropin, inhibin, estradiol, testosterone, anti-müllerian hormone, and lactate dehydrogenase. These non-epithelial ovarian tumors are rare, and the associated biomarkers should only be measured in selected clinical situations. Patients with evidence of estrogen (i.e., heavy postmenopausal

bleeding) or androgen (i.e., virilization) excess may have a steroid-secreting sex-cord stromal tumor and should have relevant hormones and inhibin measured. Given the rarity of germ cell tumors in older women, routine measurement of human chorionic gonadotropin and alpha fetoprotein is not recommended.

5.3.4 Multiple Biomarker Tests

There has been considerable interest in combing serum biomarkers in order to better distinguish benign and malignant adnexal masses. The Risk of Ovarian Malignancy Algorithm (ROMA) is a commercially available test which combines CA 125, HE4, and menopausal status to calculate the likelihood of finding malignancy in a woman with an ovarian mass. In some studies, the performance of ROMA has exceed that of either HE4 or CA 125 alone in predicting the risk of malignancy in women scheduled to undergo surgery, though this has not been universally replicated.

Another commercially available test using multiple biomarkers is OVA1. This assay measures five serum proteins (CA 125, beta-2-microglubulin, transferring, transthyretin, and apolipoprotein A1) and uses proprietary software to calculate a risk index for malignancy. This test has been studied among women scheduled to undergo surgery for an adnexal mass and was demonstrated to be superior to CA 125 alone in detecting early-stage malignancy.

It is important to note that both the ROMA and the OVA1 tests are approved for, and have been studied among, women with adnexal masses whose initial evaluation led to a plan for operative management. These tests are used to stratify risk of ovarian cancer among women scheduled for surgery to triage those at highest risk for referral to a gynecologic oncologist. The utility of these tests to determine whether a woman with an ovarian mass requires surgery has not been studied, and the use of these test is not recommended in this context.

5.4 Radiologic Studies

Radiologic studies are essential in evaluating the possibility of malignancy or acute pathology warranting intervention in women with an ovarian mass. While imaging modalities have undergone extensive innovation, ultrasonography remains the first-line imaging modality for adnexal masses and is frequently the only needed radiologic study. Other modalities including computed tomography (CT) and magnetic resonance imaging (MRI) may be utilized when sonographic assessment is equivocal or to identify and characterize metastatic disease. There is currently no role for positron emission tomography (PET) in the evaluation of an adnexal mass.

5.4.1 Pelvic Ultrasound

Gray-scale ultrasonography is the most frequently used imaging modality for assessing a pelvic mass. Combining abdominal and vaginal images produces excellent anatomical visualization and delineates important morphologic characteristics of pelvic masses. Ultrasound is widely available, relatively tolerable for patients, free of ionizing radiation, and cost-effective.

The performance of ultrasound in differentiating benign and malignant masses is operator dependant. While very experienced operators may correctly discriminate malignant and benign masses in more than 90 % of cases, performance declines in less experienced operators. Morphologic assessment of adnexal masses has a sensitivity of 82–91 % with a specificity of 68–83 % for detecting malignancy (Agency for Healthcare Research and Quality, 2006).

Mass volume, wall structure, presence and structure of septa, fluid complexity, presence of solid components, and echogenicity are sonographic features that are frequently used to determine the nature of an ovarian mass. Multiple scoring systems, using various morphologic characteristics, have been proposed for quantifying the risk of malignity of a mass (Ferrazzi et al. 1997). These systems have tended to perform better on initial report than in validation studies, and studies comparing scoring systems have found no difference in performance. In practice, many sonographers rely on subjective impression and pattern recognition rather than objective scoring systems.

Color Doppler ultrasound is utilized to characterize tumor vascularity and may be used adjunctively with morphologic assessment (Antonic et al. 1996). Malignant masses are more vascular than benign masses as a result of tumor-related angiogenesis. The blood flow characteristics of a mass can be described subjectively or quantified using a variety of indices. However, there is considerable overlap in vascular features of benign and malignant masses, and Doppler studies alone are inferior to morphologic assessment in discriminating among masses. The addition of color Doppler studies to gray-scale ultrasound appears to improve the specificity of sonographic detection of malignant masses (Bonilla-Musoles, 1993).

5.4.2 Computed Tomography

Many asymptomatic adnexal masses are recognized on CT scans obtained for unrelated indication. Computed tomography is not, however, recommended for the evaluation of most adnexal masses. There is little evidence that CT is either more sensitive or specific for malignancy than ultrasound, and CT requires the administration of ionizing radiation and, often, nephrotoxic contrast media. If suspicion of ovarian cancer is very high, CT is useful in assessing the presence and extent of metastatic disease. Furthermore, when ovarian metastasis from another site is suspected, CT can be used to identify the site of primary disease.

5.4.3 Magnetic Resonance Imaging

Magnetic resonance imaging provides excellent characterization of soft tissue and can identify fat, fibrous tissue, blood, and vascularized tumor. Administration of intravenous gadolinium is particularly useful in distinguishing fibrinous debris and organizing clot from papillary projections within a complex adnexal mass. Despite the attractive features of MRI, the use of this modality adds substantial cost to the evaluation of adnexal mass, and most masses are well characterized with pelvic ultrasound. Studies comparing the performance of MRI with US have demonstrated that MRI has similar sensitivity for identification of malignant lesions and improved specificity. As such, MRI may be an appropriate second-line test among women with sonographically indeterminate lesions. In pregnant patients, with an adnexal mass, MRI, rather than CT, is the imaging modality of choice when cross-sectional imaging of the abdomen is needed.

6 Management

6.1 Conservative Management

Conservative management is preferable to surgical intervention in asymptomatic women with benign adnexal masses (Liu et al. 2011). Prior to undertaking conservative management, the malignant potential of a mass should be assessed incorporating the patient's personal and family history, physical exam findings, radiographic characteristics of the lesions, and any laboratory testing. Furthermore, the benefits of a definitive histological diagnosis, and potential for early intervention, should be weighed against the potential risks of surgery on a case-by-case basis. In older women, conservative management consists of serial ultrasound surveillance. In women undergoing conservative management of adnexal masses with sonographic surveillance, growth or increasing complexity should prompt surgical intervention.

Most adnexal masses in premenopausal women are benign and should be managed conservatively. Functional cysts, including follicular cysts, corpus luteum cysts, and hemorrhagic cysts, are the most common lesion in menstruating women. These lesions can have a variety of sonographic appearance and can be managed with repeat pelvic ultrasound 6 weeks after diagnosis to demonstrate resolution. The most common neoplasm in premenopausal women is a mature cystic teratoma (dermoid). This benign tumor often contains fat, calcifications, and hair and can be reliably identified by ultrasound. While mature cystic teratomas have traditionally been excised to rule out malignancy and prevent risk of torsion, the risk of malignant transformation in dermoid cysts is low (0.2 %), and conservative management, with yearly sonograms to exclude rapid growth, is a reasonable option for smaller lesions.

Among menopausal women, conservative management is especially appropriate in asymptomatic women with low-risk masses including simple unilocular cysts and cysts with thin septations that are smaller than 10 cm in diameter (Saunders et al 2003). Such lesions are associated with an exceedingly low risk of malignancy. While the optimal surveillance interval is unknown, very low-risk lesions are commonly followed with a pelvic ultrasound 3–6 months after diagnosis. Tumor growth or newfound complexity should prompt surgical intervention. The surveillance interval may be lengthened in women with stable or regressing lesions. While some cystic lesions will resolve over time, the majority persist for longer than 1 year.

Cystic ovarian masses with solid component, and solid masses, have traditionally been considered high risk for malignancy and managed surgically. However, results from large screening studies have demonstrated that the vast majority of these lesions are benign. Furthermore, there is now evidence that complex masses can also be managed conservatively in the short term, though with a degree of caution (Pavlik et al. 2013). To qualify for conservative management, a woman with a complex cystic or solid ovarian mass must be asymptomatic, without evidence of metastatic ovarian cancer, and should have a normal CA 125. An ultrasound and CA 125 should be repeated within 4–6 weeks of diagnosis. Increasing size or complexity or a rising CA 125 should prompt surgical intervention. Continued surveillance is indicated in stable or resolving lesion. The surveillance interval may be lengthened once improvement is demonstrated to every 3–6 months. Interestingly, complex lesions that resolve do so more quickly than simple cysts, with a median time to resolution of approximately 9 weeks.

There is little role for drainage of cystic adnexal masses. Drainage of a malignant mass may increase the risk of dissemination and should be avoided. Additionally, cytological examination of cyst fluid is not sensitive or specific for malignancy. In women with a symptomatic cystic lesion, drainage is associated with a high risk of recurrence and surgical management superior. Drainage may be considered in symptomatic women who are not operative candidate.

6.2 Operative Management

Symptomatic masses require expedient evaluation and management. Ectopic pregnancy and ovarian torsion often require surgical management and are discussed elsewhere. Due to the increased risk of underlying malignancy in postmenopausal women, tubo-ovarian abscesses should not be managed conservatively or with image-guided drainage as is frequently done in younger women. Rarely, malignancy can present with acute symptomatology if the mass has caused torsion, or rupture. These patients may have peritoneal signs and marked tenderness and usually require urgent surgery.

Patients without immediate indication for surgery who have highly suspicious masses should be referred to a gynecologic oncologist. Outcomes of cytoreductive and staging surgery are superior when performed by a specialist (Junor et al. 1999). When the initial surgery is performed by a surgeon specializing in surgery for gynecologic malignancies, women with early-stage ovarian cancer are more likely to undergo complete surgical staging which consists of bilateral salpingo-oophorectomy, total hysterectomy, omentectomy, pelvic and para-aortic lymphadenectomy, and peritoneal biopsies. Staging allows for accurate determination of prognosis and selection of appropriate adjuvant therapy. Women with advanced stage disease whose initial operation is performed by a gynecologic oncologist have superior survival than those who have surgery performed by a general gynecologist or general surgeon. The American Congress of Obstetrics and Gynecology and Society for Gynecologic Oncology criteria for referral to a gynecologic oncologist are listed in Table 2.

It is important to exclude a non-gynecologic primary malignancy prior to undertaking surgery for a suspicious adnexal mass. Gastrointestinal malignancies and breast cancer are the most frequent tumors to metastasis to the ovaries. In the evaluation, a suspicious adnexal mass should

include screening for these common malignancies prior to surgical intervention, as identification of a non-gynecologic primary malignancy may substantially alter management.

Women with evidence of metastatic ovarian cancer should undergo surgery by a vertical midline laparotomy. Cytoreductive surgery is undertaken for advanced disease and consists of total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of all macroscopic disease. Some women with advanced ovarian malignancy may be candidates for neoadjuvant chemotherapy and subsequent surgery.

Laparoscopy is the preferred approach for excising a benign adnexal mass (Havrilesky et al. 2003). Compared to laparotomy, laparoscopic management decreases time to recovery, postoperative pain, and risk of surgical site infection. In postmenopausal women, salpingo-oophorectomy rather than ovarian cystectomy should be preformed. Intraoperative rupture and spillage of cyst contents may result in disease dissemination if the mass is ultimately found to be malignant. Thus, care should be taken to avoid spillage, and intra-abdominal morcellation, or breaking apart of the mass to aid in removal, should be avoided. It is common to use an endoscopic bag for removal of an adnexal mass to reduce the risk of dissemination.

If the primary indication of surgery is to exclude malignancy, intraoperative frozen section and histopathologic analysis may be obtained. Intraoperative pathology is generally accurate with a sensitivity of 89 % and specificity of 98 % for ovarian cancer, though variation in performance may exist across institutions (Covens et al. 2012). Intraoperative frozen section is most useful if a surgeon trained to perform ovarian cancer staging is available for intraoperative consultation should malignancy be detected. Like cytoreduction, staging of presumed stage I ovarian cancer is conducted via a vertical midline laparotomy. Though several small studies have reported success with laparoscopic staging, there is currently insufficient evidence to support routine laparoscopic staging in ovarian cancer.

7 Conclusions

Ovarian masses are a common, usually incidental, finding among older women. Most adnexal masses are benign, and many will resolve spontaneously. However, older women, particularly postmenopausal women, are at increased risk of ovarian cancer. The evaluation of an older woman with an adnexal mass seeks to identify women at high risk of malignancy for surgical intervention, while avoiding surgery in women with benign processes. Women at especially high risk of ovarian cancer should be managed by a physician specializing in the care of women with ovarian malignancies.

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Management of Pelvic Pain in Older Women

Pouya Javadian and Mikio A. Nihira

Contents

Abstract

Chronic pelvic pain (CPP) is defined as intermittent or constant pain in the lower abdomen or pelvis for at least 6 months in duration, with subsequent impact on the ability to attend to daily living activities. Gynecologists have traditionally focused on the organ-specific approach or viscera to explain or identify the pain source. It is important to recognize that as many as 55 % of women presenting with CPP will have no well-defined etiology following completion of all investigations. CPP is fairly common, with an estimated prevalence of 3.8 % in the adult female population. It is the impetus for 10 % of gynecologic referrals, 12 % of hysterectomies, and 40 % of laparoscopic procedures. The socioeconomic CPP cost is considerable, with estimated direct health care cost of $880 million per year in the United States, besides $2 billion dollars direct and indirect costs annually. Of these women, 15 % report missing work, and 45 % note experiencing reduced productivity.

This chapter will provide a comprehensive summary of chronic pelvic pain management in older women for the generalist and to facilitate appropriate investigation and management

Keywords

Chronic pelvic pain • Pelvic congestion syndrome • Physical therapy

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1 Introduction

Chronic pelvic pain (CPP) is estimated to disable one in six adult females. It causes significant limitations on the ability to work which impacts the economy at large (Zondervan et al. 2001). Consensus CPP definitions typically include (1) lower abdominal pain lasting at least 6 months, (2) excluding malignancy, (3) chronic inflammatory bowel diseases, or (4) pregnancy, and (5) limited to only during menstruation or sexual intercourse. It is often debilitating and difficult to treat. The total expenditure involved in the treatment has been estimated to be more than $2.8 billion in direct and greater than $555 million in indirect costs (Mathias et al. 1996). The CPP's impact promotes efforts of systemic evaluation, accurate diagnosis and application of different, and combined therapies from the first presentation. CPP frequently results from multiple coexisting conditions such as chronic pelvic inflammatory disease, adhesions, interstitial cystitis, pelvic congestion syndrome, endometriosis, adenomyosis, and such musculoskeletal conditions as fibromyalgia (Table 1). In contrast to chronic pain, acute pain is useful, signaling tissue damage, and prevents further damage from occurring. Sometimes, however, the sensation of pain outlasts the expected time of tissue healing, which leads to a more chronic condition. In some cases, this may be due to continued disease activity and tissue damage; yet, in other instances, it is postulated that alterations in the central nervous system (central sensitization) produce the sensation of pain in the absence of a peripheral noxious input. Neuroimaging studies have demonstrated central changes in patients with a variety of chronic pain conditions; however, without large, longitudinal studies, it is not possible to know whether these changes are a pain's cause or a consequence. The challenge is to identify those at risk of developing a chronic pain condition before such symptoms occur. In combination with an understanding of the factors precipitating the development of chronic pain, this situation could result in the design and implementation of preventive strategies.

Although the exact etiology remains unclear, CPP should be treated as a symptom with a number of contributory factors rather than as a diagnosis in itself. Because of CPP's multifactorial nature, it is critical to identify and address all contributing aspects rather than assigning causality to a single pathology. Therapies include invasive and noninvasive modalities. Invasive therapies include surgical procedures, nerve blocks, and neurostimulation, whereas noninvasive therapies include physical therapy, dietary modification, pharmacologic therapies, and behavioral therapy as shown in Fig. 1.

2 Clinical Assessment

Chronic pelvic pain's multifactorial nature can bridge specialties and make it difficult to establish a diagnosis. Adequate time should be given for the initial assessment of women with chronic pelvic pain. Patients should be encouraged to talk about their symptoms and ideas regarding causation because they often have an existing theory about the pain's source. Important information about the context of the pain, its effects on their life, and beliefs about its cause and prognosis are more likely to be gleaned when they are allowed to tell their story at their own pace (Vincent 2009). If the patient's expectation at the time of consultation can be elicited, personalized plans of assessment and treatment can be more effectively developed, empowering patients to communicate and subsequently provided with the professional care necessary to help them understand and manage their pain. Sometimes multiple visits may be required to obtain a complete history and perform a physical examination. It is helpful to provide this expectation to patients as soon as CPP is detected. A multidisciplinary approach to chronic pain has been shown to be effective in improving the social functioning as well as in reducing subjective pain measures (Flor et al. 1992). Generally, CPP assessment needs to follow identification of predisposing risk factors, chronic pain mechanisms for ongoing discomfort, and evaluation of associated visceral and musculoskeletal

Table 1 Chronic pelvic pain and etiologies

Gynecological	Gastrointestinal	Urological	Neurological	Musculoskeletal
Endometriosis	Irritable bowel syndrome	Interstitial cystitis	Pudendal neuralgia	Fybromyalgia
Adenomyosis	Inflammatory bowel disease	Urethral syndrome	Trigger points	Osteoporosis
Chronic pelvic inflammatory disease	Celiac disease	Painful bladder syndrome	Nerve entrapment	Tumors
Pelvic congestion syndrome	Constipation			Scoliosis/ kyphosis
Adhesions				Trigger points
Residual ovary syndrome				Piriform syndrome
				Hernia

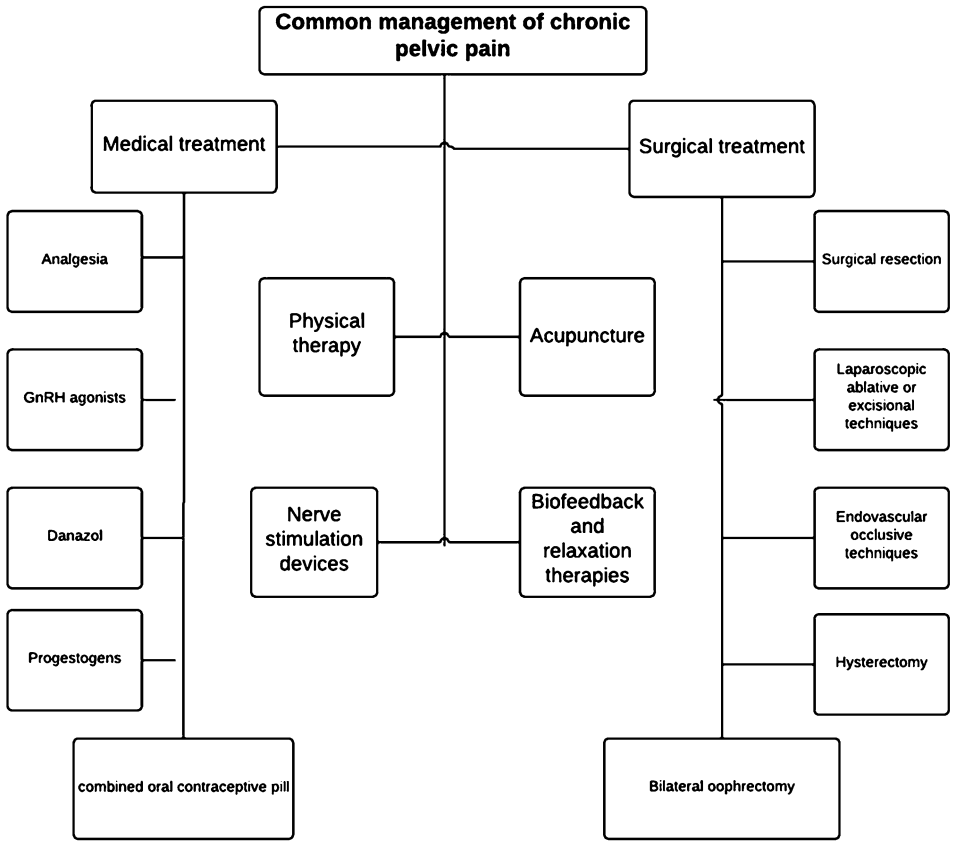

Fig. 1 Common management of chronic pelvic pain algorithm

dysfunctions and the emotional, behavioral, sexual, and social consequences. Recently, a six-point strategy for phenotyping patients with urological pelvic pain has been suggested (Nickel et al. 2009) which includes urinary, psychosocial, organ specific, infection, neurological/systemic, and musculoskeletal tenderness. This method highlights the importance of individualizing treatment plans. Women with chronic pain in general are more likely to report physical or sexual abuse

as children than pain-free women. Moreover, it appears that child sexual abuse may be a marker for development of depression, anxiety, or somatization, which then predisposes the individual to the development or presentation of chronic pelvic pain. Depression and sleep disorders are common in women with chronic pain. This may be a consequence rather than a cause of their pain, but specific treatment may improve the woman's ability to function. Women with chronic pain are more likely to report abuse (physical, sexual, emotional) than pain-free women. Physicians should be aware of the possibility of continuing abuse as well as the local legal requirements of reporting.

Because often there is pain involved when performing an examination, working with CPP patients often requires more time. Physicians should begin with observation, including gait and posture with precise inspection for skin alterations or damage. Abdominal and pelvic examinations should focus on abnormalities such as focal tenderness, enlargement, distortion, and tethering or graft prominence or exposure. Transvaginal ultrasound (TVS) can be useful not only in identifying and assessing the ultrasound morphology of the adnexal masses but also the mobility and relative tenderness of the pelvic floor muscles and viscera. It is also useful in identifying such structural abnormalities as hydrosalpinges or fibroids, which may be relevant even if these are not suspected to be the leading cause of pain. Additionally, it is useful in identifying ovarian endometriomas and adenomyosis but fails to identify peritoneal endometriosis (Shobeiri et al. 2012). New technologies including 3D endovaginal ultrasound have proved to be a useful tool for pelvic floor exam in the everyday clinical environment (Shobeiri et al. 2012) especially in the cases that involve patients that have had polypropylene mesh inserted into their vaginal wall to treat stress urinary incontinence of pelvic organ prolapse. Magnetic resonance imaging (MRI) has been demonstrated to be more sensitive and specific to the adenomyosis diagnosis. The role of MRI in diagnosing small deposits of endometriosis is uncertain; however, it may be useful in the assessment of palpable nodules in the pelvis or when symptoms suggest the presence of rectovaginal disease (Heilbrun et al. 2010).

Diagnostic laparoscopy has been considered the "gold standard" method for diagnosis in CPP for years because it successfully identifies endometriosis, adhesions, dilated pelvic veins, and ovarian pathology. However, laparoscopy involves a number of risks, with large series quoting approximately 3 % risk of minor complications and 0.6–1.8/1,000 risk of major complications such as bowel perforation and vascular damage.

Furthermore, a negative diagnostic laparoscopy is not always reassuring to the woman and may reaffirm her beliefs that the doctors think that the pain/discomfort is psychological. Therefore, the likelihood of a negative finding should be discussed with the patients. Screening for sexually transmitted infections should be considered in all sexually active women with chronic pelvic pain. A 2007 national survey of Americans aged 57–85 found that the majority of older Americans are sexually active (Today's Research on Aging 2009). A positive endocervical sample only supports but does not prove the diagnosis of pelvic inflammatory disease (PID), and thus, systemic evaluation and different as well as combined diagnosis strategies are required.

3 Management Strategies

Diagnosis should be based on the associated pathologies, and management strategies should be started by targeting the underlying pathological cause. It should be kept in mind that the pain management itself should not be delayed for the diagnosis of causative factors and should be addressed with targeted treatment for the pathology. Appropriate analgesia should be offered to patients to control their pain even if other therapeutic maneuvers are yet to be initiated. If opioids or other scheduled drugs are required, a referral to pain management should be considered. A multidisciplinary team needs to discuss all options and plans with the patient.

4 Pelvic Inflammatory Disease (PID)

PID is characterized by infection and inflammation in the women's upper genital tract. A PID diagnosis is based on the clinical findings and requires a high index of suspicion. It is caused by sexually transmitted infections such as *Gardnerella vaginalis*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*, plus anaerobic vaginal microbes. Chronic PID can cause CPP. In practical terms, the key physical examination components include (i) abdominal examination, vaginal speculum examination, bimanual examination for assessing cervical motion, uterine or adnexal tenderness, and pelvic masses and (ii) microscopic evaluation sample of cervicovaginal discharge for assessing *Trichomonas vaginalis*, bacterial vaginosis (BV), and/or leukorrhea (Mitchell and Prabhu 2013). In England, between 2000 and 2009, diagnoses of sexually transmitted infections in adults over age 45 doubled to almost 13,000 cases. In the United States, the Centers for Disease Control and Prevention statistics documented there were 706 diagnoses of infectious syphilis among adults aged 45–54 and 179 in those aged 55–64 in 2000. For chlamydia, there were 5,601 diagnoses in adults aged 45–54 and 1,110 in adults aged 55–64 in 2000, but by 2010, this had risen to 16,106 and 3,523, respectively. Similarly, in Canada between 1997 and 2007, gonorrhea cases among adults aged 40–59 increased from 379 to 1,502, chlamydia cases increased from 997 to 3,387, and infectious syphilis from 34 to 527 cases. In comparison with an increase in syphilis in adults aged 15–29 from 36 to 248 (BC Centre for Disease Control 2014).

The reason for such increases is unknown. Older women are more vulnerable physiologically. Postmenopausal changes to the vagina, such as thinning of the mucosa, narrowing and shortening of the vagina, and decreased lubrication leave women more susceptible to minor genital injuries and micro-abrasions that facilitate the entry of pathogens. After the menopause, vaginal pH increases from 3.5–4.5 to 5.0–7.5, and a higher vaginal pH has been associated with an increased risk of contracting chlamydia and gonorrhoea.

The therapeutic goal for the treatment of PID is both short-term microbiologic and clinical cure and long-term prevention of injury, namely, tubal infertility, ectopic pregnancy, and chronic pelvic pain. Among the patients who qualify for outpatient therapy, if no meaningful clinical response is detected within 72 h or sooner, these patients may require hospitalization, transition to parenteral antibiotics, further diagnostic tests including imaging to evaluate for possible tubo-ovarian abscess, and possible surgical intervention.

5 Adenomyosis

Adenomyosis is a prevalent, benign disorder in which the endometrial glands and stroma invade the myometrium, either diffusely or focally. Some 30–50 % of women with adenomyosis are asymptomatic. The cause of adenomyosis is unclear, but the overall frequency and intensity of the reported symptoms are correlated with the severity of the adenomyotic lesions (Vercellini et al. 2006). Evidence suggests that the disease is associated with the chronic disruption of the margin between the basal layer of the endometrium and myometrium, allowing significant invasion of the endometrial glands and stroma into the myometrium. Obtaining a thorough and accurate history can provide initial clues to identifying adenomyosis. On physical examination, women with adenomyosis often have diffusely tender uteri and suffer from symptoms like menorrhagia, dysmenorrhoea, CPP, and deep dyspareunia. Such high-resolution imaging techniques as ultrasound and MRI have allowed significant advances in diagnosing adenomyosis. A computed tomography (CT) scan has a much more limited role in the diagnosis of adenomyosis (Levy et al. 2013). It is often difficult to make a firm adenomyosis diagnosis, and there is little risk involved in treating it on the basis of type and severity of symptoms. Thus, after ruling out other, more serious conditions such as endometrial cancer, it is appropriate

to offer these women several options based on either a definitive or presumed adenomyosis diagnosis. Combined oral contraceptives, progestogens, gonadotropin-releasing hormone agonists, nonsteroidal anti-inflammatory drugs (NSAIDs), valproic acid, tranexamic acid, and LNG-IUS (Mirena) are considered as potential medical treatments. For some women, particularly those who are close to menopause, expectant management is appropriate while awaiting the cessation of menses and troublesome symptoms. Other women, who are comfortable with sterilization may elect for hysterectomy if attempts at, ultimately, hysterectomy is the only cure available.

6 Gastrointestinal Causes

Patients with an "irritable bowel syndrome" (IBS) as seen by gastroenterologists are presenting with symptoms suggestive of chronic pelvic pain in gynecological practices. These patients are frequently younger ages; however, IBS accounts as a notable part of pelvic floor pain in women. This raises the question whether IBS and CPP are two separate disease entities with mutual high comorbidity. This syndrome is part of a global and integrated concept of pelvic-perineal dysfunction, avoiding a rigorous distinction between the posterior and the midline and anterior segments of the perineum. It has been shown that almost half of the patients with CPP who treated laparoscopy and 40 % of patients who had opted for an elective hysterectomy had symptoms compatible with the diagnosis IBS (Longstreth 1994). These conditions may be a primary chronic pelvic pain cause, a chronic pelvic pain component, or a secondary effect caused by an efferent neurological dysfunction in the presence of chronic pain. With respect to comorbidity in IBS and CPP, it has to be kept in mind that while IBS comorbidity studies can be qualified and based on an international consensus, such precise diagnostic criteria does not exist for CPP. IBS and chronic pelvic pain share a common pathophysiology rather than being distinct clinical entities in the general population; notably, somatization appears to be the link. IBS treatments begin dietary modifications and/or first-line medications contingent on the patient's symptoms and level of severity. Several treatment options have been proposed, ranging from diet to pharmacology and psychotherapy, and are available. Treatment of abdominal pain, gas, and bloating may be initiated with dietary adjustments of carbohydrates and fat intake. Dicyclomine and hyoscyamine as antispasmodic agents can in the short term provide improvement. Unfortunately, such products cause anticholinergic side effects and cannot be tolerated for long-term use. Fiber and laxatives relieve chronic constipation, despite having limited data on their efficacy. Tegaserod, a 5-hydroxytryptamine receptor 4 (HT4) agonist, has demonstrated to be effective in the improvement of symptoms related to constipation-predominant IBS. This medication is now limited to compassionate use due to increase in cardiovascular events. First-line treatment of IBS-related diarrhea is loperamide. Alosetron, a 5-HT3 antagonist, is also useful as an antidiarrheal.

In contrast, bulking agents and stimulant laxatives may lead to aggravate other IBS symptoms such as cramping and flatulence. Psychosocial aspect of IBS can be treated with selective serotonin reuptake inhibitors which have been reported to improve IBS patient's quality of life and provide a global benefit without significantly altering bowel symptoms or decreasing pain. Their usefulness in this setting may be secondary to an underlying somatization disorder, a characteristic that has been attributed to both IBS and CPP patients (Matheis et al. 2007).

7 Urological Causes

Interstitial cystitis (IC)/painful bladder syndrome (PBS) was described as "the complaint of a suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of urinary infection or other obvious pathology"(Rourke et al. 2014). The diagnosis is partly based on the exclusion of other diseases and is often based on a "clinical principle," which is an informal consensus among urologists that may or

may not be based on evidence from within the medical literature. The uncertain PBS etiology made it very difficult to classify it. Although the mechanisms involved are not understood well, there are number of theories and risk factors proposed.

Genetic factors are considered as important risk factor responsible for PBS based on the high prevalence in first-degree relatives. This has been illustrated in a study with 25,000 twins, with strong genetic component as the PBS etiology. Furthermore, strong study on both environment and genetic factors on both monozygotic and dizygotic twins confirmed the same result.

In a PBS survey conducted with women, previous surgery found was a statistically significant risk factor. They state that there is a high chance that the reason for the pelvic surgery is a confounding factor. Infection (urinary tract infection (UTI)) has been shown to be present in 18–36 % women at the onset of PBS. The hypothesis is based on either the body's response to infection is the initiator of the process or the UTI causes a physiological response that result in PBS. Another postulated etiology is glycosaminoglycans (GAGs) disruption. GAG is a protective bladder's surface layer. It has been reported that a deficiency in GAGs increases the sensitivity of the bladder wall and BPS. Intravesical hyaluronan treatment is postulated to support the GAG layer and has been observed to result in successful treatment of PBS. Nitric oxide (NO) metabolism is another proposed mechanism of pathology. NO has an important role in bladder filling control by nerve modulating in rats. Adenosine triphosphate (ATP) release through NO signaling may play a major role in the hypersensitivity of PBS. Bladder urothelium is responsible for NO release which has fundamental role in overactive detrusor activity, which has been observed in PBS sufferers (Rourke et al. 2014).

The poorly understood etiology of PBS has brought about many different treatment and management options. They include different types of behavioral, dietary, interventional, pharmacologic, and surgical therapies (Rourke et al. 2014). Conservative therapy options should be exhausted before providing less reversible surgical therapies. An initial therapy for PBS should focus on educating the patient and providing them with an understanding of the common exacerbating factors and treatment options. It has been mentioned (Hanno et al. 2011) that the behavior modification can improve the symptoms and, therefore, should be the first line of treatment. Patients should be told to avoid certain foods and drink, commonly coffee and citrus products as these are probable irritants. Certain types of exercises, sexual intercourse, stress, tight-fitting clothing, and constipation may also act as exacerbating factors in some patients. Relieving factors should be explained such as local heat or cooling over the bladder region and pelvic floor relaxation exercises. Treatments include oral therapy, intravascular, intravesical, and surgical therapies. Oral pentosan polysulfate (PPS) is the only oral medication approved by the United States Food and Drug Administration (FDA) for PBS. Analgesics are an important part in the management process; however, it is not sufficient and other treatment avenues should be explored. Gabapentin, in combination with amitriptyline and NSAIDs, have shown considerable promise in reducing the symptoms after 4 weeks of treatment. Tanezumab is a proposed intravascular drug, which is composed of anti-inflammatory agents. It has been reported to have 50 % or greater reduction in pain. Intravesical therapies included dimethyl sulfoxide, heparin, Bacillus Calmette-Guerin (BCG), liposomes, hyaluronic acid, and chondroitin sulfate. Based on an uncertain etiology of PBS/IC, a multimodal approach should be applied, and monotherapy with the above agents is therefore not advocated. Botulinum toxin, Hydrodistention, transurethral resection, sacral neuromodulation, and cystoplasty are surgical options for patients. However, expectations should be made clear to patients that these surgical interventions may not completely relieve the pain caused by PBS (Hanno et al. 2011).

8 Musculoskeletal Causes

Musculoskeletal causes are increasingly being recognized as a contributor to pelvic pain in women. The prevalence of such pain is estimated to be as high as 75 % in a pelvic pain clinic (Slocumb 1984). Pelvic floor muscle disorders (PFMD) are major contributors to a multitude of dysfunctions, with one recent study suggesting that the increase in the demand for care of PFMD is predicted to increase by 35 % in the next 17 years, with >1.6 million patient visits predicted for the year 2030 (Kirby et al. 2013). Two common musculoskeletal causes of pelvic pain are myofascial pain syndrome and pelvic floor tension myalgia. These two conditions are often unrecognized and misdiagnosed. The pathophysiologic mechanism is not fully understood, but there are multiple risk factors that must be evaluated. Studies have revealed a high prevalence of primary or secondary musculoskeletal abnormalities in women with chronic pelvic pain. Visceral pain, orthopedic pathology, direct trauma, and psychosocial stressors may trigger discomfort in the abdominal wall and pelvic floor. Physical examination can help to differentiate the pain sources. Carnett's test is a useful exercise to assess the abdominal myofascial involvement. Briefly, Carnett's sign is a finding on clinical examination in which (acute) abdominal pain remains unchanged or increases when the muscles of the abdominal wall are tensed. For this part of the abdominal examination, the patient can be asked to lift the head and shoulders from the examination table to tense the abdominal muscles. Alternatively, ask the patient to raise both legs with straight knees. A pelvic organ prolapse and injury to the levator ani have also been described as the cause of pain. A pelvic organ prolapse, presented as herniation of the pelvic organs against the vaginal walls and often through the vaginal introitus, is noted as a defect in support of vaginal walls, which are held in place by connective tissues and the pelvic musculature. Advancing age, obesity, connective tissue disorder, and parity beyond one pregnancy could be possible risk factors. A spasm of the pelvic floor muscles has also been described as a cause of pain, which can be reduced by the botulinum toxin injection. Musculoskeletal treatment approaches are based on their underlying cause. Using injections (e.g, lidocaine, bupivacaine, and botulinum toxin A) have demonstrated an improvement in pain management. For the pelvic organ prolapse, patients may choose to receive conservative treatment, physical therapy, surgical repair, or observe the condition. For surgical correction, patients should be referred to a subspecialty practice such as urogynecology or to a gynecologist experienced in the surgical management of prolapse.

9 Physical Therapy Intervention

Pelvic floor exercises and biofeedback try to reestablish the resting tonus of the pelvic floor muscles and improve their function. When pelvic floor dysfunction (PFD) progresses to a myofascial pain syndrome, directed physical therapy is advised to reestablish coordinated dynamic and resting behavior. Myofascial pain syndrome is the end result of long-standing stress, with high tone on a specific muscle group resulting in shortened myofibrils.

American Physical Therapy Association (APTA) stated that the physical therapy interventionists' goal is to restore normal function of pelvic floor while working to reduce any negative psychological impact associated with the disease, pain, or dysfunction being addressed (Hartmann and Sarton 2014). In this setting, physical therapists bring a broad approach to the management of chronic vulvar and pelvic pain. They utilize a variety of manual therapy techniques to treat comorbid conditions of pelvic floor dysfunction (PFD), including biofeedback.

Women's health physical therapists need to address emotional issues associated with chronic pain, including sexual dysfunction. It will be much less successful if the treating therapist is unable or unwilling to discuss sexual function as she goes through her chosen treatment protocol. Intervention is driven by organ system dysfunction and physical findings. Through the

assessment process, abnormal physical findings need to be examined for full pelvic health recovery. To address physical findings, manual therapy including modalities like soft tissue mobilization, myofascial release, joint manipulation, visceral mobilization, therapeutic exercise, and neural mobilization can be used to correct musculoskeletal dysfunction throughout the body as well as within the pelvic cavity. Physical therapies always include an exercise prescription with home exercise program designed to improve core stability and correction of any gait or postural imbalances as indicated.

10 Pelvic Congestion Syndrome (PCS)

Pelvic congestion syndrome (PCS) is a common cause of disabling chronic pelvic pain in women of child-bearing age and occurs when varicose veins develop around the ovaries in a CPP setting. It has been estimated that as many as one third of women with CPP have congested pelvic veins as a comorbid condition. The underlying cause is pelvic venous insufficiency (PVI) which is defined as the incompetence of the ovarian vein or internal iliac vein or both. Furthermore, asymptomatic women have also been found to have pelvic varicosities (Nascimento et al. 2002), making PCS a challenging disorder to diagnose. There are nonspecific associated symptoms including depression, headache, lower backache, rectal discomfort, and bloating. Pregnancy and previous pelvic surgery are known to act as associated risk factors.

Pelvic pain is thought to result from engorged ovarian and pelvic veins. The activation of selective pain receptors of the venous walls results in a diffused arch through the viscera. Imaging techniques can confirm the pattern of the varicosities in the setting of pelvic symptoms. A CT scan and MRI can identify the pathology. Venography has been considered as the "gold standard" assessment of pelvic vein congestion and provides an option of performing interventional treatment if needed. PCS treatment is a 2-step process involving selective embolization of the ovarian vein(s) and balloon occlusion sclerotherapy of the internal iliac veins. Ovarian vein embolization is feasible through advancing the catheter to close proximity to the associate para-uterine varicosities. Embolization materials including vascular occlusion devices and liquid or foamed sclerosants can be used via popular technique called "sandwich" to occlude the varicose vein. Briefly, sandwich technique is the mechanical occlusion of the proximal and distal ends of the ovarian vein (Phillips et al. 2014).

11 Pain After Surgery

Patients with a chronic pain condition are more likely to develop postoperative pain, and many women with CPP will have had operations previously, increasing their risk of complications. Pain control studies after gynecologic surgery are limited, and those pertaining directly to urogynecologic procedures are desperately sparse. Poor postoperative pain control during the postoperative period cause heightened sympathetic discharge, which increases the risk for myocardial infarction and stroke. This also leads to decreased ambulation, with resultant increased risk for thromboembolism, and poor inspiratory effort, which leads to increased risk for postoperative pneumonia. Lastly, poor acute postoperative pain control can lead to central sensitization with resultant chronic pain sequelae.

Multimodal analgesic approaches should be considered for all procedures because they have been shown to improve postoperative pain relief as well as reduce opioid requirements and opioid-related adverse effects. Perioperative paracetamol, NSAIDs, dexamethasone, and local anesthetic techniques have shown to improve postoperative pain relief.

In patients with vaginal surgery for prolapse or incontinence, infiltration of local anesthetic into the posterior vagina and perineum reduces postoperative pain. Pudendal blockade may also be considered for improved early postoperative pain control. Postoperative pain management of patients with abdominal urogynecologic procedures includes bilateral transversus abdominis

plane (TAP) block. The TAP blocks may not be necessary for laparoscopic procedures because the pain from the port-site incisions may be adequately managed by wound infiltration.

Although opioid analgesic medications have always been the mainstay of postoperative pain management, this review reveals that many other pain control strategies are effective after gynecologic surgery. Augmenting the current pool of resources for controlling pain after urogynecologic surgery may significantly improve the patient experience at the time of surgery for pelvic floor disorders (Collins et al. 2014).

12 Adhesions

Adhesions are a common occurrence in women with and without pelvic pain. These may be caused by earlier infections such as appendicitis or pelvic inflammatory disease, endometriosis, and previous surgery. Not all adhesions cause pain; however, two distinct cases where adhesions are particularly known to cause pain are ovarian remnant syndrome and trapped ovary syndrome. The vascular adhesions may cause CPP particularly when the ovarian tissue is involved. Although the association between the adhesions and pain is still unclear, there is no evidence to support the division of fine adhesions in women with chronic pelvic pain and relief pain, except in women who have dense, vascular adhesions involving the bowel. In case of ovarian entrapment, the GnRH analogue or ovarian tissue removal is likely to be benefitted. Overall, there is no conclusive evidence to support the division of fine adhesions in women with CPP (Hindocha et al. 2015).

13 Endometriosis

Endometriosis is traditionally the most common cause of chronic pelvic pain and is usually cyclical. It happens in women in their reproductive age; however, in older women in premenopausal period, there is still chance of endometriosis. In severe cases, the pain is not confined to the pelvis and may involve the bladder and bowel. The pain is not always cyclical and is often in the lower back. Endometriosis is the presence of ectopic endometrial tissue in the extrauterine sites; however, the precise pathogenesis of endometriosis is unknown. Retrograde menstruation, altered immunity, metaplasia of the germinal epithelium, stem cell, and genetic origins are reported as the pathogenesis behind the disease. Abdominopelvic pain is reported in 58 % of women with endometriosis. Diagnostic laparoscopy is known as the definitive diagnosis of endometriosis. Transvaginal ultrasonography has shown to reliably identify endometriomas. For cases with subperitoneal endometriotic deposits, MRI is a better diagnostic tool.

Medical and surgical interventions are treatment recommendations dependent on the patient's symptoms, severity, medical history, age, and reproductive age. Medical therapies aim to reduce pain and disease activity by ovarian suppression including hormonal replacement therapy, medroxyprogesterone acetate, cyproterone acetate, or dienogest, for pain associated with endometriosis. Although the androgenic steroid danazol and antiprogesterone gestrinone were previously the most prescribed drugs for endometriosis, they should be avoided as their androgenic side effects outweigh benefits. Gonadotropin-releasing hormones such as GnRH agonists are considered as the second-line therapy. NSAIDs and the combined oral contraceptive pill (COCP) have been shown to be effective in relieving pain in primary dysmenorrhoea.

Surgical treatment of endometriosis aims to remove all areas of ovarian and deep infiltrating endometriosis, particularly when the disease affects the bowel and other organs as there might be associated morbidity. Advancements in surgical tools help in a better excision of the diseased area rather than just ablation. Laparoscopic treatment results in improved pain outcome. Studies showed that in cases with endometriosis greater than 3 cm in diameter, excisional surgery leads to a better outcome than ablation considering the recurrence of pain and endometrioma (Brawn et al. 2014).

14 Conclusion

In conclusion, pelvic pain is a common symptom in women that is challenging to manage. The average gynecologist will encounter many women with this condition over the course of their career. CPP is a difficult condition for patients and clinicians alike: Insufficient understanding of the problem's precise etiology and sometimes multifactorial nature leads to complex treatment strategies. The assessment process should allow enough time for the woman to be able to tell her story. This may be therapeutic in itself. Because pain is subjective, a pain diary may be helpful in tracking symptoms or activities associated with the pain. Identifying the primary cause of the pain, it is clearly important that the secondary consequences (be they musculoskeletal, psychological, gastrointestinal, sexual, etc.) must also be managed, and this is best done within a multidisciplinary setting. It is important to consider psychological and social factors as well as physical causes of pain.

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Management of Sexual Dysfunctions

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Abstract

Female sexual disorders are common. Despite their prevalence, clinicians often feel they are inadequately prepared to address the needs of women with sexual complaints.

The aim of this chapter is to highlight and review the diagnosis and management of sexual dysfunction in women, including how to take a thorough history, perform a targeted physical examination, and order appropriate laboratory testing to help determine etiology. Diagnostic algorithms and treatment options are reviewed.

Keywords

Female sexual dysfunction • Women • Female sexual interest/arousal disorder • Female orgasmic disorder • Genito-pelvic pain/penetration disorder

1 Introduction

Millions of women in the USA experience sexual problems at some point in their lives. However, only one-third of women suffering with seriously distressing sexual problems seek professional help for their concerns. Of those, the majority bring their complaints to primary care physicians and gynecologists. Thus, it is important for providers to be familiar with the varying presentation of female sexual dysfunction and to attain the necessary skills to screen patients, make an accurate diagnosis, and initiate appropriate treatment. They should also be prepared to refer refractory or complex cases to sexual medicine specialists.

2 Definition and Classifications

Female sexual dysfunction (FSD) is defined as any problem or disturbance during any stage of the sexual response cycle (desire, arousal, orgasm, and intercourse) that causes significant distress in a woman's daily life and relationships. The definition and classification of female sexual dysfunction disorders continue to evolve. Currently, three major classification systems exist: the World Health Organization's International Classification of Disease (ICD-10), the classification proposed by the American Foundation of Urologic Disease (AFUD), and the classification defined by the American Psychiatric Association's Diagnosis and Statistical Manual of Mental Disorders, which was recently updated as the DSM-V (Chen et al. 2013).

Prior to the DSM-V, the DSM-IV-TR was used to define and diagnose sexual dysfunction in women and included disorders of sexual desire (hypoactive sexual desire disorder or HSDD and sexual aversion disorder), sexual arousal (female sexual arousal disorder (FSAD)), orgasm (female orgasmic disorder), and sexual pain (dyspareunia and vaginismus). These disorders were primarily based on the traditional concept of a linear sexual response. However, research has shown that the sexual response of women is not always a linear, uniform process and that distinction between certain phases of sexual response (e.g., desire and arousal) may not be valid; the new DSM-V criteria were proposed to reflect this shift in thinking. DSM-V aimed to improve the precision of female sexual dysfunction diagnoses by adding a minimum requirement of 6-month duration for the symptoms, in an attempt to avoid overdiagnosis. In this chapter we will refer to the DSM-V criteria, because this is the most current classification system in use.

On the basis of DSM-V diagnostic criteria, female sexual dysfunction (FSD), which is not caused by an organic disorder or disease, may be divided into three major categories:

1. *Female sexual interest/arousal disorder (FSIAD)*

   The new DSM-V criteria merged sexual desire and sexual arousal disorders into one category, now called female sexual interest/arousal disorder (FSIAD), which is defined as the presence of three of the following six criteria for a minimum duration of approximately **6 months**:

- Persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts
- Absent/reduced interest in sexual activity
- No/reduced initiation of sexual activity and typically unreceptive to a partner's attempts to initiate
- Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately, 75–100 %) sexual encounters (in identified situational contexts or, if generalized, in all contexts)
- Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual)
- Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (approximately 75–100 %) sexual encounters (in identified situational contexts or, if generalized, in all contexts)

To be classified as FSIAD, the symptoms should cause clinically significant distress in a woman's life and cannot be attributed to a nonsexual mental disorder or be a consequence of severe relationship distress (e.g., partner violence) or other significant stressors and also cannot be attributable to the effects of a substance/medication or another medical condition.

FSIAD can be further specified according to the duration of the onset, frequency, and severity of symptoms:

- **Lifelong:** The disturbance has been present since the individual became sexually active.
  Or
- **Acquired:** The disturbance began after a period of relatively normal sexual function.
  And
- **Generalized:** Not limited to certain types of stimulation, situations, or partners.
  Or
- **Situational:** Only occurs with certain types of stimulation, situations, or partners.
  And
- **Mild, moderate, or severe:** Based on evidence of mild, moderate, or severe distress in response to the symptoms.

2. *Female orgasmic disorder (FOD)*

Female orgasmic disorder (FOD) is defined by the presence of one of the following:

- Inability to reach orgasm after adequate sexual arousal and stimulation
- Infrequent or delayed orgasm
- Reduced intensity of orgasmic sensation

These symptoms should be present for **at least 6 months** on all or almost all (approximately 75–100 %) occasions of sexual activity and cause significant individual distress. Orgasmic disorder can be further specified as acquired or lifelong, generalized or situational, and mild, moderate, or severe.

3. *Genito-pelvic pain/penetration disorder*

Genito-pelvic pain/penetration disorder (GPPD) represents the merging of the prior DSM-IV sexual pain disorder (vaginismus, recurrent involuntary spasm of the musculature of the outer third of the vagina, and dypareunia, genital pain associated with intercourse) categories. GPPD is the presence of at least one of the following:

- Difficulty in vaginal penetration
- Marked vulvovaginal or pelvic pain during vaginal intercourse or attempt at penetration
- Marked fear or anxiety about pain in anticipation of, during, or after penetration
  And/or
- Marked tightening or tensing of pelvic floor muscles during attempted penetration

These symptoms must cause significant distress for at least 6 months and should not be a result of another nonsexual mental disorder or the consequence of a severe relationship distress (e.g., partner violence) or other significant stressors and should not be attributable to the effects of a substance/medication or another medical condition.

GPPD can also be categorized as acquired or lifelong, generalized or situational, and mild, moderate, or severe.

2.1 Prevalence

As the largest US survey on women's sexual problems, the PRESIDE study (Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking) queried 30,000 women using validated questionnaires. In this study, the prevalence of low desire, low arousal, and difficulties with orgasm showed that the prevalence of any of these three sexual problems (with or without distress) was 43 %; 22 % reported sexually related personal distress and 12 % attributed distress to a specific type of sexual problem (e.g., desire) (Shifren et al. 2008).

Lack of desire was the most commonly reported sexual problem in women. While reported by 39 % of women, it was sufficiently severe to cause distress in 10–14 %. Low arousal (26 %) and difficulties with orgasm (21 %) were slightly less prevalent and were associated with distress in 5 % of the cases. Five percent of women reported both low desire and another sexual problem; 2 % reported all three problems (Shifren et al. 2008).

2.2 Etiology

Female sexual disorders, like many other medical problems, often do not have a single cause. They are likely associated with a combination of factors, such as biological, psychological, and social influences.

1. **Biological**

   Age has been shown to be correlated with the likelihood of FSD. The prevalence of all classes of FSD (except GPPD) increases substantially with age. Although aging is known to cause physical and hormonal changes, the sexual behavior of midlife and older women is highly dependent on several factors such as general physical and mental well-being, quality and duration of relationships, and life situation. Sex hormones, particularly low levels of estradiol, can contribute to the lack of sexual interest and to the presence of vaginal dryness and atrophy in naturally menopausal women. In addition to hormonal alterations, psychosocial and interpersonal factors, medication use, and associated illnesses are factors that may intensify the effects of aging on sexual function in women. However, sexuality and sexual function remain an important aspect of life for many older women. In women aged 50–60 years, 65 % reported on sexual desire and almost 48 % had at least three episodes of sexual intercourse per month (Safarinejad 2006).

   In addition to aging, chronic illnesses such as diabetes, hypertension, rheumatologic disorders, or presence of other serious medical conditions (such as cancer) may impair a woman's sexual function because of psychosocial changes associated with the condition as well as the condition itself (Buster 2013).

   Furthermore, some other physical problems make sexual activity uncomfortable including endometriosis or atrophic vaginitis. Chronic pelvic pain, uterine fibroids, interstitial cystitis, and pelvic inflammatory disease can cause deep dyspareunia. Superficial dyspareunia on the other hand is usually related to vestibulodynia and vulvodynia. Localized vulvodynia or vestibulodynia is pain that is caused by touching a localized area of the vulva, commonly occurring in the region of the vestibular glands. It can also occur at the clitoris, clitorodynia, or on one side of the vulva. The pain is often described as a feeling of burning, stinging, tearing, throbbing, or being cut by razor blades or glass.

   Women with vaginismus may demonstrate high pelvic floor muscle tension and/or experience genital pain and/or report fearing vaginal penetration or pain that makes vaginal penetration impossible. Some women, however, may not feel pain. For some, vaginismus is limited to sexual activity. Vaginismus is frequently linked with female sexual interest/arousal disorder and sexual aversion. In other cases vaginismus is linked with gynecologic

disorders, such as vestibulitis or endometriosis, chronic medical conditions, or drugs and responds to treatment for those problems.

2. **Psychological**

   Psychiatric problems, including mood disorders such as depression and/or anxiety, can be associated with impaired sexual function. Many psychotropic medications used to treat these conditions can also exacerbate sexual problems. Trauma, such as a history of prior physical or sexual abuse, can also contribute to sexual dysfunction.

3. **Social**

   Fatigue, stress, lack of privacy, and conflict within an intimate relationship can impair sexual functioning. Factors such as lower educational levels, financial dependence, and poor health have all been shown to be correlated with a significant increase in risk of FSD.

3 Screening

Ideally, women should be queried about sexual health concerns at regular intervals. Practices can adopt intake forms that include questions about sexual function as part of their review of systems. There are several validated questionnaires that can be used as screening tools including the Female Sexual Function Index (FSFI). The FSFI is a brief, 19-item questionnaire that assesses multiple dimensions of female sexual function, including sexual satisfaction.

Typically, a general routine health encounter does not provide adequate time for a thorough evaluation of sexual concerns. To insure that they are appropriately addressed, a follow-up visit should be scheduled to provide dedicated time to focus on these issues.

A diagnostic algorithm based on the recently released DSM-5 classification system and the latest recommendations of the International Consensus of Sexual Medicine is presented to assist with evaluation of patients with sexual complaints (Fig. 1; Latif and Diamond 2013). This tool contains various questions about sexual complaints that practitioners can ask to assist with the diagnosis of a particular sexual disorder.

4 History

The evaluation of sexual dysfunction in women begins with a comprehensive medical history. The clinician should ask about the duration of symptoms as well as their severity and the setting in which the symptoms most frequently occur. Initial questions should be open-ended questions, such as, "Many people have concerns about sex and sexual health; do you have any questions or concerns that you would like to discuss?" Open-ended questions should be followed by silences that encourage the patient to speak and then by directed questions that should be asked (American Psychiatric Association 2013).

As sexual problems may be difficult for some women to discuss, it is important to use words and body language that put the patient at ease. Maintaining an open, nondefensive body posture can help facilitate communication. The clinician should sit down and should maintain eye contact and choose language that is appropriate to the age, ethnicity, and culture of the patient.

A complete medical and medication history is elicited in order to identify organic, psychological, and medication or substance-related issues that may affect sexuality (e.g., depression, diabetes, use of selective serotonin reuptake inhibitors). Any suspicion of an undiagnosed medical or mental illness should be followed by further evaluation or referral.

(a) **Gynecologic history**

A gynecologic history and review of systems should include symptoms and conditions that might affect sexual activity or signal the need for further evaluation; this includes information about menopausal status (natural, surgical, or post-chemotherapy); pregnancy and childbirth history and history of pelvic injury, cancer, or surgery; vulvovaginal or pelvic pain and vulvovaginal pruritus, dryness, or discharge; abnormal genital tract bleeding; and urinary or fecal incontinence (Latif and Diamond 2013).

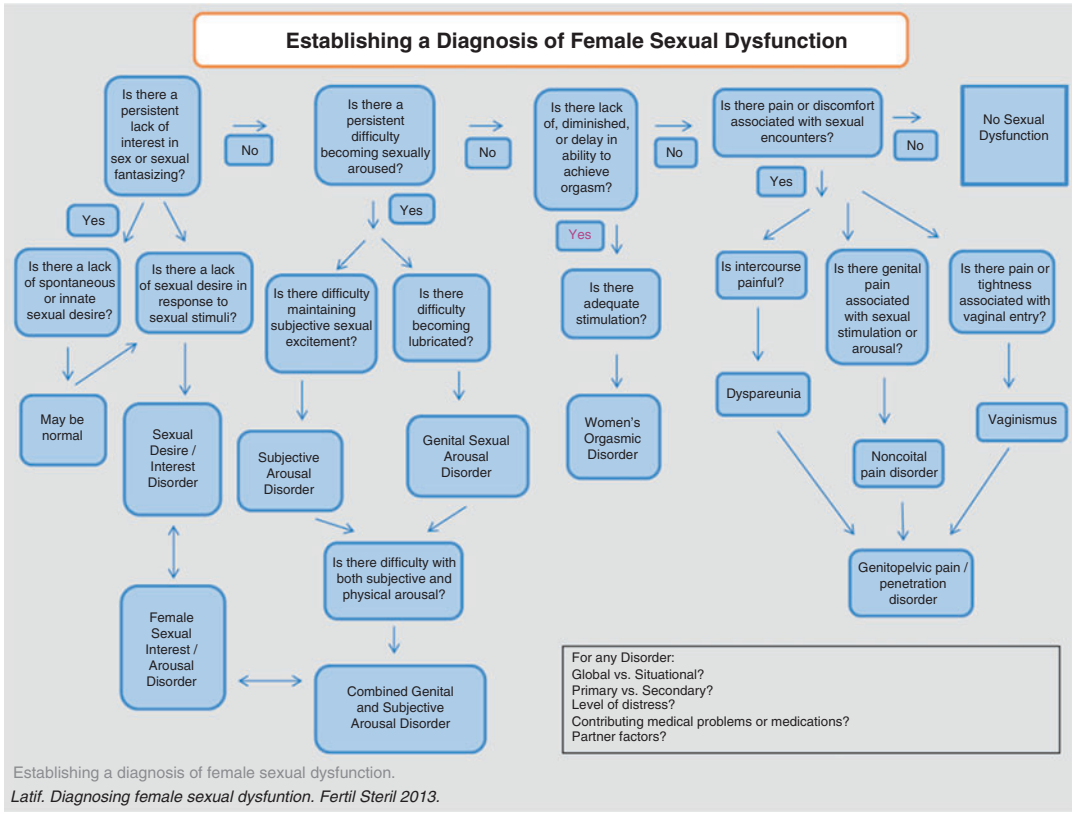

Fig. 1 Evaluation of patients with sexual dysfunction. Originally published in Latif and Diamond (2013); with kind permission of © Elsevier® 2013. All Rights Reserved

Multiple gynecologic factors have been found to be associated with sexual function. It has been reported that low desire or dyspareunia is a common finding in postpartum women. However, there is no evidence of long-term differences among women with vaginal vs. cesarean delivery. Greater parity does not appear to be related to low sexual desire or sexual satisfaction (Rosen and Simon 2014). Nevertheless, delivery of a newborn and infertility are risk factors for sexual dysfunction.

Coital pain is more prevalent in young women than in older women, perhaps because of the presence of higher-tone pelvic floor musculature, which can result in pain during sexual activity. Weak pelvic floor muscles are associated with urinary incontinence and pelvic organ prolapse. Sexual dysfunction is reported in 20–40 % women with urinary incontinence. In women with pelvic organ prolapse, the rate of sexual complaints appears to be higher than in others with no prolapse. Since muscular dysfunction may be directly responsible for the symptoms related to sexual function, health professionals who treat symptoms related to pelvic floor dysfunction should also screen for sexual dysfunction, which enables them to offer the most comprehensive treatment options (Serati et al. 2009).

(b) **Sexual History**

Additionally detailed questions regarding the onset of the current symptoms as well as changes in frequency and severity should be addressed. Gender and number of partners, types of sexual practices, and past sexual history with the current or previous partners should be discussed.

History of rape, domestic violence, and childhood sexual abuse can have significant

effect on one's sexual health, and patients are most often uncomfortable to disclose. Providers should deliberately address these traumatic life events.

(c) **Medical history**

Chronic underlying medical illnesses can be associated with female sexual dysfunction. For instance, thyroid problems are associated with distressing desire problems in younger patients (Nusbaum et al. 2004). In addition to thyroid disorders, other endocrinologic and non-endocrinologic disorders (such as diabetes, hypopituitarism, Cushing disease, hypertension, arthritis, and inflammatory or irritable bowel disease) are associated with an increased risk for sexual problems. Some of the more common medical conditions associated with FSD are discussed below:

1. **Diabetes**: The effect of diabetes on female sexual functioning is uncertain. Hyperglycemia, which is a main determinant of vascular and microvascular diabetic complications, could potentially explain the pathogenic mechanisms that could cause sexual dysfunction in diabetes. Poorer levels of sexual functioning may be seen in diabetic women with peripheral neuropathy. While one study found reduced genital sensation in women with diabetes, studies comparing sexual dysfunction in women with and without diabetes have yielded inconsistent results (Maiorino et al. 2014). In addition, people with diabetes often present with multiple medical comorbidities, including hypertension, obesity, metabolic syndrome, tobacco use, and atherogenic dyslipidemia, which are themselves risk factors for sexual dysfunction.
2. **Hypertension:** Sexual dysfunction is common in hypertensive patients. Available data indicates that sexual dysfunction is more frequent in treated than in untreated patients, generating the hypothesis that antihypertensive therapy might be associated with sexual dysfunction. Hypertension-related atherosclerosis, endothelial disorder, and antihypertensive drugs are important risk factors for female sexual dysfunction. The negative effects of beta-blockers on male sexual function are well known; some data suggest that beta-blockers also have a detrimental effect on female sexual function. Studies have reported that the risk of sexual dysfunction was greater in hypertensive women treated with beta-blockers than in those treated with other agents (Duncan et al. 2000).
3. **Neurologic conditions:** Neurological conditions and their treatments have been shown to be associated with sexual dysfunction. Specifically, spinal cord injury, the use of antiepileptic drugs in epileptic patients, multiple sclerosis, and Parkinson's disease are all associated with sexual dysfunction.
4. **Cancer:** The sexual consequences of multiple types of cancer and their treatments have been documented. Fatigue associated with treatment, reactive depression, anxiety, and changes in body image following surgery on the breasts or pelvic organs may contribute to sexual dysfunction in women with cancer (Falk and Dizon 2013). Breast cancer is the most common cancer in women in the USA. Sexual dysfunction following breast cancer is prevalent, with multiple issues contributing to the problem. In addition to changes in body image, hormonal therapy such as the use of aromatase inhibitors can have vast implications for sexual functioning by contributing to vulvar and vaginal atrophic changes.

(d) **Psychiatric history**

Sexual dysfunction is increased among patients with psychiatric disorders and may be related to both the psychiatric condition and its medical treatment. A significant association has been reported between psychiatric problems and all aspects of FSD. Psychiatric diseases may increase the risk of SD, and SD may further exacerbate psychiatric problems, suggesting a bidirectional relationship. The persistence of sexual problems can have a significant negative impact on a patient's

satisfaction, adherence to the treatment, quality of life, and partnership.

Depression and its associated drug therapy are some of the most common psychiatric factors that inhibit sexual function. Depression is present in 17–26 % of women who complain of low sexual desire. SD may be aggravated by antidepressants, especially selective serotonin reuptake inhibitors (SSRIs). Selective serotonin receptor inhibitors (SSRIs) can cause low desire and difficulty with orgasm in women.

The negative symptoms of schizophrenia limit the capability for interpersonal and sexual relationships (Zajecka 2001). First-generation (typical) antipsychotic medications may lead to sexual dysfunction by affecting dopamine and prolactin levels. Dopamine serves as a central neuromodulator of sexual function and acts as the only inhibitor of prolactin release from the anterior pituitary. First-generation (typical) antipsychotic medications block dopamine receptors and may give rise to hyperprolactinemia. High levels of serum prolactin lead to gonadal suppression. Second-generation (atypical) antipsychotic medications (e.g., aripiprazole) raise prolactin levels to a lesser degree than first-generation antipsychotics (e.g., olanzapine or risperidone) and thus may have less impact on sexual function (Reichenpfader et al. 2014).

(e) **Medication history**

Many over-the-counter and prescription drugs may affect sexual function in women. Thus, a thorough review of a patient's current and recent medication use is necessary. Table 1 demonstrates some of the most common medications that may cause sexual dysfunction.

5 Partner Assessment

Since relationship factors are a principal determinant of sexual satisfaction for women, women with partners should be asked about the status and quality of their intimate and sexual relationships. A patient should also be asked about whether her partner has sexual issues (e.g., lack of desire or erectile dysfunction). Studies of sexual function in older women have revealed that a common reason for sexual inactivity was not having a partner or having a male partner with sexual problems. As erectile dysfunction in men increases with aging, and women typically live longer than men, the "partner gap" becomes a major cause of sexual dissatisfaction for older women.

6 Physical Examination

A complete physical examination, which includes a pelvic examination, is important to identify any pathology and determining potential causes of sexual dysfunction. The clinician should search for evidence of vaginal atrophy, dryness, and pain-triggering spots. A pelvic examination is indicated to confirm a normal pelvic anatomy, evaluate for genital or pelvic tenderness or lesions, assess for pelvic organ prolapse or vaginal atrophy, and follow up on concerns raised by the medical history (e.g., vaginal discharge or abnormal genital bleeding). The clinician should refer the patient to other health professionals if she/he does not have the time or expertise required to perform a proper evaluation.

7 Laboratory Evaluation

Laboratory testing should be performed if indicated by history and/or examination and may include cervical cultures for gonorrhea and chlamydia, complete blood count, thyroid stimulation hormone (TSH), and measurement of prolactin levels. Androgen levels should not be used to determine the cause of a sexual problem, as serum androgen concentrations do not appear to be an independent predictor of sexual function in women (Rivera-Woll et al. 2004). An endocrine evaluation in appropriately selected patients may include measurement of the serum follicle-stimulating hormone, luteinizing hormone, serum estradiol, dehydroepiandrosterone, total testosterone, free testosterone, and prolactin levels.

Table 1 Drugs associated with sexual dysfunction. Medications that cause sexual dysfunction. Originally published in Conaglen and Conaglen (2013); with kind permission of © Australian Prescriber 2013. All Rights Reserved. (Conaglen and Conaglen 2013)

Drug class	Decreased desire	Decreased arousal	Orgasm or ejaculatory difficulties
Antidepressants	Amitriptyline Clomipramine Fluoxetine Imipramine Paroxetine Phenelzine Sertraline	Amitriptyline Citalopram Clomipramine Doxepin Fluoxetine Imipramine Nortriptyline Paroxetine Phenelzine Sertraline Tranylcypromine	Citalopram Clomipramine Doxepin Escitalopram Fluoxetine[a] Fluvoxamine Imipramine Nortriptyline Paroxetine[a] Sertraline[a] Tranylcypromine Venlafaxine
Other psychotropic drugs	Alprazolam Chlorpromazine Fluphenazine Haloperidol Lithium Risperidone	Chlorpromazine Fluphenazine Lithium Risperidone	Alprazolam Fluphenazine Haloperidol Risperidone
Cardiovascular drugs	Clonidine Digoxin Hydrochlorothiazide Methyldopa Spironolactone	Beta-blockers Clonidine Digoxin Hydrochlorothiazide Methyldopa Perhexiline Spironolactone	
Other drugs	Cimetidine	Antihistamines Cimetidine Cyproterone Disulfiram Gonadotrophin-releasing hormone Agonists Propantheline Pseudoephedrine	Naproxen

[a]Common cause of orgasmic difficulty

8 Advanced Testing

In certain cases a pelvic or transvaginal ultrasound may be necessary to assess pelvic anatomy and rule out underlying structural pathology. Measures of genital blood flow, vaginal wall compliance, and genital vibratory sensation thresholds are experimental procedures that may be used in specialized clinics and research settings to study and help diagnose sexual dysfunction and monitor treatment efficacy. Other advanced sexual health evaluations performed by sexual medicine specialists may include vulvoscopy, vaginal photoplethysmography (measurement of vaginal vasocongestion), biothesiometry, and perineometry (assessment of pelvic floor musculature).

9 Treatment

Treatment of female sexual dysfunction can be challenging. FSD is usually multifactorial, and physicians have limited expertise in the treatment

of female sexual dysfunction. Treatment should be tailored to address causal factors (Latif and Diamond 2013).

9.1 Educating Patients on Sexual Health

Educating the patient and her partner about "normal" sexual response and anatomy is often necessary, especially as it relates to major life events such as childbirth and menopause. Addressing a patient's fears or concerns about sexual dysfunction and educating her about sexual health can help improve the patient's receptiveness to treatment and increase her overall knowledge. It is important to discuss any obvious reversible causes of FSD and encourage adoption of lifestyle changes that may be beneficial to sexual functioning, such as stopping smoking, eating a healthy diet, exercising regularly, and reducing stress. Efforts should also be made to improve communication and intimacy in relationships.

9.2 Assess the Patient's Goals

After the cause or causes of the patient's sexual dysfunction have been identified, it is important to determine what the patient is expecting to accomplish with treatment and use her goals to evaluate progress. This gives the clinician the opportunity to set realistic goals, clarify any misconceptions about treatment, and allow for progress to be more accurately measured. While some women may desire modest improvements in their sexual life, others may expect that treatment will allow them to achieve an ideal based upon past experience or cultural images of sexuality.

9.3 Optimizing General Health

Some patients experiencing sexual dysfunction have other underlying medical issues such as depression, substance abuse, or drug side effects. Many physical and psychological conditions are associated with sexual dysfunction. Often, treating these underlying conditions or adjusting medication and dosing may lead to improvements in sexual function. For example, women with depression who are experiencing sexual side effects when taking a selective serotonin reuptake inhibitor (SSRI) can sometimes be treated with a different class of antidepressant. Identification and treatment of substance abuse, as well as the underlying factors that precipitated it, often result in improved sexuality and overall quality of life.

9.4 Use a Team Approach

Sexual disorders can be complex and their treatment can be time intensive and require special expertise. Despite this complexity, gynecologists can offer initial treatment that improves sexual function. Other experts may sometimes be needed to address underlying physical and psychological factors; referral to psychotherapists, sex therapists, or pelvic physical therapists may be warranted. With the patient's consent, communication and management decisions should be shared between the patient's clinician and other health-care providers who treat the patient (e.g., cardiologist, psychiatrist, etc.). This communication is important when trying to find a treatment strategy that works best for the patient. It can also be useful to involve the patient's partner in the treatment, especially if relationship therapy is needed or the partner's sexual dysfunction is contributing to that of the patient.

9.5 Make a Treatment Plan

The ultimate goal of therapy is to utilize interventions that address and optimize the biological, psychological, and social factors that contribute to sexual satisfaction. Treatment options range from sexual health counseling to pharmacologic interventions and surgery.

9.6 Treatment of Female Sexual Interest/Arousal Disorder

Treatment of female sexual interest/arousal disorder should be based on its identifying causes. Both pharmacologic and non-pharmacologic options are available.

9.6.1 Non-pharmacologic

Counseling may help patients deal with underlying psychological or relationship issues. Couple's therapy and/or sex therapy may improve communication and decrease conflict within the relationship that contributes to sexual dysfunction. Given the efficacy and high degree of safety of sex therapy, it is reasonable to refer women with no obvious biological pathology to a sex therapist prior to initiating a trial of pharmacologic therapy.

9.6.2 Pharmacologic

Sexual desire and arousal are facilitated by neural, vascular, and hormonal phenomenon. Women's arousal is associated with increased blood flow to the vagina and clitoris that results in clitoral erection, vaginal engorgement, changes in vaginal luminal diameter, and vaginal lubrication. Phosphodiesterase type 5 (PDE5) inhibitors have been widely used for the treatment of erectile dysfunction; although the physiologic effects of PDE5 inhibitors are similar in males and females, results in women have been conflicting (Schoen and Bachmann 2009).

Sex steroids (estrogens, progestogens, and androgens) play a crucial role in modulating neuroendocrine and neurovascular responses to sexual stimuli. Many older women report decreased interest or arousal but have underlying dyspareunia. In older women, estrogen depletion may affect sexual desire indirectly through reduction of genital secretions and pelvic muscle elasticity. Hormone therapy can potentially improve sexual function in postmenopausal women but results have been conflicting. (Martins et al. 2014)

Low-dose vaginal estrogen therapy alone is highly effective in treating atrophic changes and dyspareunia and may lead to improvement of sexual interest, arousal, and satisfaction with sexual activity. Bremelanotide (Palatin) is a melanocortin receptor (MC3R and MC4R) agonist that is in phase 3 trials for the treatment of FSIAD. Preliminary studies have demonstrated efficacy in the treatment of this disorder.

Female aging is associated with a decline in endogenous androgen production. Female sexual interest/arousal disorder is seen in patients who have undergone bilateral oophorectomy or have premature ovarian failure, panhypopituitarism, or adrenal insufficiency, as all of these conditions are associated with decreased androgen production. Treatment with androgen replacement (such as testosterone gels, implants, patches, etc.) can induce sexual desire in women. Transdermal testosterone (IntrInsa, Watson Pharmaceuticals/Theratech and Procter & Gamble) in physiologic to slightly super-physiologic doses (300 microgram/day) was previously shown to result in increased sexual activity and pleasure (Basson et al. 2000; Rosen and Simon 2014). While this product was previously approved for use in Europe, it failed to gain FDA approval in the USA. Potential side effects of the use of testosterone include acne, hirsutism, and masculinization. Despite frequent off-label use of topical testosterone for FSD, its use remains controversial, because of long-term safety concerns with regard to risk of breast cancer and cardiovascular disease.

In June 2015, the FDA advisory committee approved flibanserin for the treatment of hypoactive desire disorder. Flibanserin is a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist. It is postulated to work by improving the balance between the excitatory effect of dopamine and inhibitory effect of serotonin in the neurotransmitter systems (Allers et al. 2010). Three major clinical trials have reported statistically significant improvement in "satisfying sexual events" (SSE) over placebo after 24 weeks of treatment with a single dose of 100 mg per day. The rate of serious adverse effects has been reported to be <0.9 %. The most common adverse effects reported in these studies are nausea, dizziness, fatigue, hypotension, and somnolence. Therefore, it is recommended that it be

taken once daily, at bedtime, to lower the risks related to sedative effects of the drug. Flibanserin is the first FDA-approved drug for the treatment of hypoactive desire disorder (now FSIAD).

9.7 Treatment of Female Orgasmic Disorder

The goal of therapy for female orgasmic disorder (FOD) is to enable the patient to reach orgasm as desired. Treatment is based on managing inciting factors, features of the patient's presentation, and any anticipated difficulties with acceptance of or adherence to treatment. In primary orgasmic disorder, treatment with directed masturbation is a first-line therapy over other interventions. Where abuse is a factor, there is evidence that psychotherapy and couple's counseling may be helpful. Secondary orgasmic disorder is often associated with female sexual interest/arousal disorder, pelvic surgery, or drugs, such as antidepressants. Treatment of the primary problem frequently leads to restoration of the ability to achieve orgasm. For women who can have orgasms through masturbation but not during partnered sexual activity (i.e., situational secondary female orgasmic disorder), education about sexual positions and activities to enhance clitoral stimulation are recommended. Cognitive-behavioral therapy, anxiety reduction with the use of behavioral exercises, sensate focus, and systematic desensitization as well as sex education, communication skills training, and Kegel exercises are other potential treatment options (Meston et al. 2004).

The Eros clitoral therapy device (Rockville, MD, USA) is a small clitoral vacuum pump that is FDA approved for the treatment of sexual dysfunction in women; it has been reported to increase sensation and intensity of orgasm and improve overall sexual satisfaction.

9.8 Genito-pelvic Pain/Penetration Disorder

Treatment for GPPPD ranges from pharmaceutical agents, biofeedback/electrical stimulation, and physiotherapy to surgery. Adherence to vulvar hygiene has been shown to be an effective initial strategy to reduce vulvar complaints of burning, itching, pain, and dyspareunia. The use of neuropathic pain modulators, including tricyclic antidepressants such as amitriptyline or desipramine, can help decrease neuropathic chronic pain through a central action altering the transmission of pain impulses to the brain through the dorsal horn. Narcotic pain medications should be avoided in patients with vulvodynia.

For vaginismus, combination of cognitive and behavioral psychotherapy, typically referred to as systematic desensitization, is thought to be an effective intervention. Some gynecologists recommend botox as an adjunct for vaginismus (Islam et al. 2001). Treatment of hypertonicity using pelvic floor physical therapy also appears to play a crucial role in reducing pain and improving sexual functioning.

10 Conclusion

Sexual concerns are common in women; thus, clinicians should be proficient at screening for sexual disorders and initiating evaluation and treatment and prepared to refer complex cases to specialists in sexual medicine. Obtaining a comprehensive history (gynecologic, medical, psychiatric, and medications) is crucial for accurate diagnosis and treatment. The treatment of female sexual dysfunction should address its underlying causes, and both non-pharmacologic and pharmacologic options are available. Psychological interventions including cognitive-behavioral therapy and sex therapy should be considered as a part of the treatment approach. The goal of treatment should be to achieve sexual satisfaction, which can ultimately improve women's quality of life and well-being.

11 Cross-References

► American Psychiatric association 2013

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Operative Hysteroscopy

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Contents

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Abstract

In this chapter, we aim to describe contemporary operative hysteroscopy. A further aim is to provide an outline for safe and effective practice when performing such procedures by summarizing the best available evidence supplemented by the authors' own experience. More specifically, this chapter will cover the available equipment, technologies, and techniques necessary to perform a variety of hysteroscopic procedures, namely, removal of fibroids and polyps, endometrial ablation, treatment of acquired and congenital uterine abnormalities, removal of placental remnants, and sterilization. We will also discuss the role of teaching, clinical governance, and audit in improving operative hysteroscopic services.

Keywords

Hysteroscopy • Vaginoscopy • Operative hysteroscopy • Outpatient hysteroscopy • Ambulatory hysteroscopy • Office hysteroscopy • Resectoscopy

1 Introduction

In 1869, the first successful diagnostic and operative hysteroscopy was performed when Pantaleoni used a cystoscope and candlelight to treat an endometrial polyp causing postmenopausal bleeding. Then in 1907, Charles David was the first to describe a lens system that allowed uterine cavity visualization. Yet, it was not until 1943 that Forestiere's cold light source and Hopkin's rod lens were combined to form the endoscopes that have become the basis for today's hysteroscopy.

With advances in technology and techniques, hysteroscopy has taken over from dilatation and curettage to become the gold-standard procedure for investigation and treatment of pathologies in the uterine cavity. It has the advantage of being able to visualize the uterine cavity directly and can sometimes allow simultaneous treatment to be performed. A large number of procedures can now be performed hysteroscopically. These include fibroid resection, polyp removal, sterilization, removal of chronically retained products of conception (RPOC), adhesiolysis, septoplasty, and endometrial ablation. Hysteroscopic surgery is minimally invasive, avoiding surgical incisions and the need for prolonged inpatient hospital stay. Furthermore, proficient operative hysteroscopy is both quick and safe. Increasingly procedures are being performed in a more convenient ambulatory or "office" setting avoiding the need for hospital admission or general anesthesia. Indeed, the concept of office-based "see-and-treat" hysteroscopy has been propagated over the last decade with simultaneous treatments being undertaken conditional upon the prior diagnostic hysteroscopy.

Although complication rates for operative hysteroscopy are low, some complications can be life threatening. It is therefore imperative that appropriate training programs are combined with an understanding of the equipment and techniques to make operative hysteroscopy a safe and efficient tool.

2 Equipment

Most operative hysteroscopes consist of an inflow channel for distension media, an outflow channel for distension media, an operating channel with a sheath to allow instrumentation, a light lead, and telescope with fiber-optic cables and a camera head (Fig. 1).

Some hysteroscopes use an angled optic that allows better visualization of the cavity. It is important to realize that when inserting the hysteroscope through the cervix, the endocervical canal is positioned at 6 o'clock if the optic is upward and 12 o'clock if the optic is downward (Fig. 2). For most hysteroscopes, the position of the light lead is the same as the location of the endocervical canal.

Light leads are fiber-optic cables that act as conduits for light between the generator and the telescope. Fiber-optic cables are prone to damage

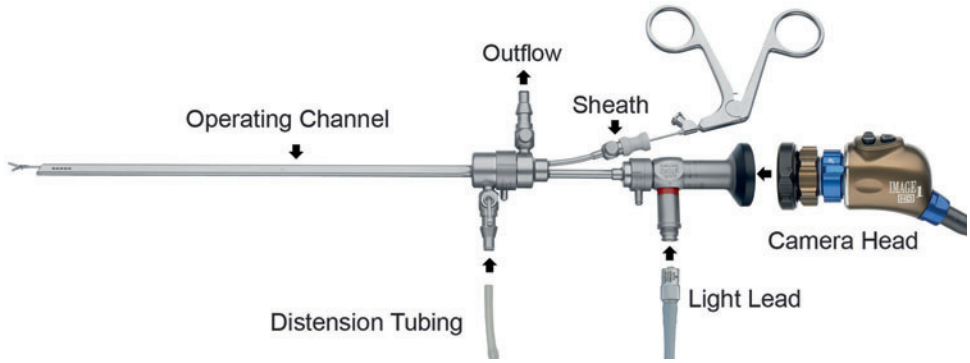

Fig. 1 Components of operative hysteroscope

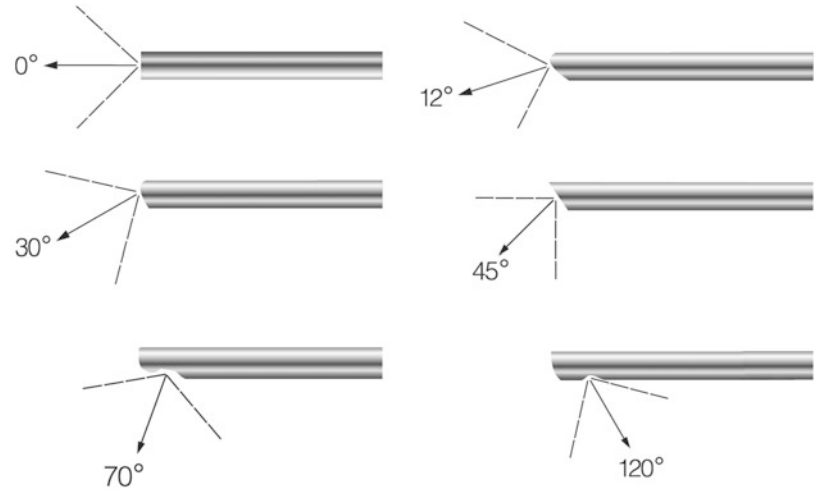

Fig. 2 Endoscopic viewing angles (hysteroscopes have a 0°, 12°, 25°, or 30°)

and are normally the cause of low light generated by the telescope. Looking for dark spots at the end of the cable can assess this.

3 Patient Preparation

An important part of patient preparation is adequate counseling about the rationale for the procedure and what it involves. The patient experience is important to describe especially for those women undergoing office-based procedures without general anesthesia. Potential complications and the expected clinical outcomes need to be discussed in a frank manner. Patient information leaflets are an essential component in preoperative counseling because they support verbal information given to further ensure that patients are adequately informed and prepared for their hysteroscopic procedure.

4 Technique

Although not always practical, hysteroscopy should be performed in the first half of the menstrual cycle when the endometrium is at its thinnest. Pregnancy should be ruled out before all cases begin. When positioning patient for hysteroscopic procedures, the patient should be in the lithotomy position with the buttocks slightly over the edge of the operating table.

4.1 Prevention of Cervical Trauma and Perforation

There is evidence to suggest the hysteroscopic procedures under direct vision are more accurate than dilatation and curettage (Loffer et al. 2000; Valle 1981). Not only should procedures under direct vision be done in preference to blind procedures for the purpose of accuracy but also for safety reasons. As further advances are made resulting in miniaturization of equipment, the need for blind dilatation, which risks uterine trauma, will also be reduced.

Cervical trauma and patient discomfort can be reduced by using the thinnest hysteroscopic equipment available and the "no touch" or vaginoscopic technique. The vaginoscopic technique is achieved by guiding the hysteroscope into the uterus under direct vision without using any potentially painful instrumentation. The easiest way to do this is to enter the vagina allowing the distension media to fill the cavity and follow the posterior wall of the vagina down into the posterior fornix. The hysteroscope is then maneuvered into the cervix above and pushed through the cervical canal into the uterus. The vaginoscopic technique can only be used for hysteroscopes less than six millimeters in diameter.

The administration of oral or vaginal prostaglandins such as misoprostol prior to operative procedures has been researched and has shown that spontaneous cervical dilatation is increased but with no decrease in complications (Cooper et al. 2011a). There are inconsistent results of the benefits of osmotic dilatators such as laminaria prior to operative procedures.

5 Distension Media

The technique of hysteroscopy requires a distension medium to be instilled into the uterine cavity to allow visualization of the uterine cavity enabling both the diagnosis and surgical treatment of intrauterine pathology. A variety of distension media can be used including liquids such as glycine, dextran, sorbitol, water and normal saline, and gases such as carbon dioxide. Comparisons of normal saline to carbon dioxide as distension media have shown no difference in pain or visualization, although procedures done with normal saline were found to be significantly faster (Cooper et al. 2011b). However, carbon dioxide is infrequently used nowadays because special insufflation equipment is needed and its use is restricted to simple diagnosis. The plethora of new therapeutic hysteroscopic systems requires fluid distension media to continuously irrigate the uterine cavity removing blood and tissue debris thereby providing a clear operative picture.

The use of isotonic fluid normal or "physiological" saline is the preferred fluid media for operative hysteroscopic procedures because inadvertent fluid overload does not lead to severe osmotic imbalance (hypervolemic hyponatremia) (Berg et al. 2009). Mechanical technologies such as tissue removal systems can be used in normal saline. When it comes to operative procedures using electrical energy, the type of distension media is dictated by whether monopolar or bipolar electrical circuits are being used. Bipolar electrodes require conductive, electrolytic solutions such as normal saline (285 mOsm/L) or Ringer's lactate (279 mOsm/L), while procedures using monopolar electrodes need nonconductive, hypo-osmolar, nonionic solutions such as glycine 1.5% (200 mOsm/L) or sorbitol 3% (165 mOsm/L).

The new generation of bipolar electrodes is generally safer than monopolar electrodes because they do not affect serum osmolality or sodium levels. However, all solutions can cause complications from intravascular absorption of large volumes of fluid into the circulatory system. Excessive fluid absorption is most likely with prolonged hysteroscopic procedures using larger diameter endoscopes with continuous irrigation of fluid or where blood vessels within the myometrium are opened. Thus, particular care is required with resection of the endometrium (transcervical resection of the endometrium – TCRE) and hysteroscopic myomectomy (transcervical resection of fibroids – TCRF). Serious complications arising from expansion of the extracellular fluid volume with the potential to generate fluid overload, pulmonary edema, include acute pulmonary edema, cerebral edema, and cardiac

failure. Therefore, it is important to accurately measure the input and output of fluid during operative hysteroscopy so that significant fluid deficits can be recognized and managed promptly. While delivery of the distension medium can be safely and effectively achieved using simple gravity or pressure bags, automated pressure delivery systems facilitate the creation of a constant intrauterine pressure and accurate fluid deficit surveillance. The American Association of Gynecologic Laparoscopy (AAGL) guidelines recommend that when fluid deficits with a nonelectrolyte solution reach 1500 or 2500 mL with normal saline, the procedure should be brought to a halt (Loffer et al. 2000).

6 Hysteroscopic Treatment of Fibroids

6.1 Submucous Fibroids

Fibroids or leiomyomas are benign overgrowths of the smooth muscle layer of the uterus. They remain the most common indication for hysterectomy. Submucous fibroids are those that protrude into the uterine cavity. They account for 5% of all fibroids. Submucous fibroids are associated with pain, bleeding, infertility, and recurrent miscarriage. The most established classification system for submucous fibroids was developed by Wamsteker and the European Society of Gynecologic Endoscopy (ESGE) and accepted by the International Federation for Obstetrics and Gynecology (FIGO) (Munro et al. 2011). This nomenclature states that if the submucous fibroid is entirely intracavitary, i.e., attached to the uterine cavity sidewall by only a small stalk, they are classified as type 0; if a portion of the fibroid is intramural, then they are type 1 if less than 50% is intramural and type 2 if more than 50% is intramural.

Submucosal fibroids can be selectively removed hysteroscopically, which is particularly useful in women who want to preserve their fertility and avoid the complications of laparoscopic or laparotomic surgery. Types 0 and 1 are suitable for hysteroscopic resection. Removal of type 2 fibroids is more challenging because risks of perioperative bleeding, incomplete removal, and uterine trauma are significantly greater. Furthermore, the need for repeated hysteroscopic or other surgical interventions are greater to treat ongoing abnormal bleeding symptoms compared with type 0 and 1 fibroids (Vercellini et al. 1999). Another classification system has been developed to describe additional prognostic features related to submucous fibroids; in addition to depth of myometrial penetration, the STEPW classification records the size, topography (location), and extension of the base in relation to the uterine wall (Lasmar et al. 2012) .

Hysteroscopic removal is mostly done with resectoscopy, i.e., electrosurgical resection using a modified urological resecting loop. More recently, hysteroscopic morcellators, now termed tissue removal systems, have been introduced offering simultaneous mechanical cutting and tissue aspiration, and these technologies appear to be gaining increasing popularity (van Dongen et al. 2008). Some surgeons did use laser hysteroscopic myomectomy in the past, but the laser units are associated with high capital and running costs and have largely been abandoned now.

6.2 Endometrial Preparation

It is common practice to give medication to suppress the endometrium and shrink fibroids prior to surgery. It is thought that this improves visualization by thinning the endometrium and helps to ensure complete removal of the fibroid. The use of gonadotropin-releasing hormone analogues (GnRHa) 3–4 months prior to surgery does reduce fibroid size and corrects anemia prior to surgery (Lethaby et al. 2001). However, data supporting the benefits of endometrial downregulation prior to operative hysteroscopy are conflicting, and currently there are no randomized controlled studies showing surgical removal, and clinical outcomes are improved by this practice (Kamath et al. 2014). Recent work has shown that the selective progesterone receptor modulator, ulipristal acetate, is an effective alternative to reduce fibroid size and induce amenorrhea prior to fibroid

surgery with fewer side effects than GnRHa (Donnez et al. 2012a, b). However, as with GnRHa, data supporting improved outcomes with hysteroscopic myomectomy are lacking.

It is important to assess the size and the degree of intramural involvement before embarking on medication to shrink the fibroids, to effectively counsel the patient and plan appropriate surgery. Transvaginal ultrasound is now common in the evaluation of women with gynecological problems, but on its own, it is not accurate enough to adequately describe protrusion of the fibroids into the endometrial cavity. The advent of the 3D ultrasound and saline infusion sonography has been shown to improve accuracy (de Kroon et al. 2003; Lee et al. 2006). Ultrasound is useful to describe the distance between the intramural component and the serosa, which can help the surgeon prevent perforation of the uterus during hysteroscopic treatment. Hysteroscopy provides the best method for assessing the degree of protrusion into the endometrial cavity and the suitability for surgery. With the advent of outpatient hysteroscopy, this can be done without subjecting the patient to general anesthesia.

6.3 Hysteroscopic Equipment for Removal of Fibroids

Hysteroscopic resectoscopes are versatile tools that consist of a movable cauterization electrode usually in the form of a loop (Fig. 3). Originally the resectoscopes used a monopolar electrode, but advances in technologies have led to the development of equally effective bipolar resectoscopes that have the increased safety advantage of using isotonic distension media with reduced risk of serious complications arising from fluid overload and hypervolemic hyponatremia

6.4 Technique

The first step is to identify all the uterine cavity landmarks, and these should continue to be visualized throughout the procedure. The surgeon should be familiar with their equipment and technology especially the angle of the offset lens, energy modality, and distension media management. The amount of fluid deficit considered reasonable, which will depend upon its nature and the patients' medical comorbidities, should be discussed between the surgical team and the anesthetist prior to commencing the procedure.

6.4.1 Electrosurgical Resection

For electrosurgical resection, the loop electrode should be extended beyond the fibroid. The activated electrode is then drawn toward the surgeon by either moving the entire hysteroscope or closing the electrode or a combination of these two movements. Usually a blended or pure cut current set at 120 W cutting is adequate. The activated electrode should never be pushed away from the surgeon as this can cause perforation. Cutting into the myometrium should be avoided, particularly near the cornua and cervix where it is at its thinnest and bleeding or uterine perforation may occur. The degree of magnification and extension of the loop from the distal lens should be adjusted according to the location of the fibroid or area

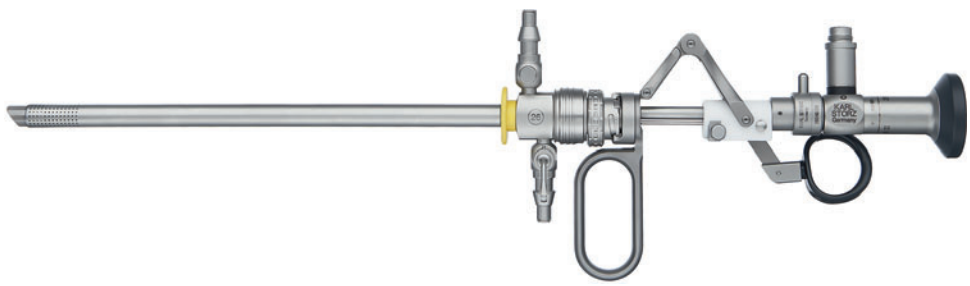

Fig. 3 Resectoscope

being resected, e.g., a higher degree of magnification (proximity of the distal lens) is needed when resecting fibroid tissue near the fundus or cornua.

One of the main disadvantages of electrosurgical resection of submucous fibroids is that as the fibroid is progressively debulked, "chips" of fibroid tissue are generated, which compromise visualization and impede the free movement of the loop electrode. One strategy to combat the impact of these fibroid chips is to push them toward the fundus to keep the view clear until enough are generated to obscure the visual field. A variety of techniques are then used to remove the chips, which include using a curette and polyp forceps or closing the inactivated resectoscope loop thus catching the chips. Also, the resectoscope can be removed from its outer sheath allowing the chips to traverse the cervical canal through the sheath.

The fibroid should be resected until it is level with the endometrium. Spontaneous uterine contractions as well as fluctuations in intrauterine pressure, e.g., increasing and decreasing the distension media pressure, can help push some of the intra-myometrial component of a grade 1/2 fibroid into the uterine cavity allowing safer resection under direct vision. Mechanical undermining of the intramural fibroid component with the passive inactivated electrode or with a firmer specially designed hook can achieve the same thing. This latter surgical approach has been described as adopting a "cold knife" technique (Mazzon et al. 2016). As the intramural extension of the capsule is reached, the myometrial sinuses are exposed which can lead to bleeding and increased and sometimes rapid intravascular absorption of fluid.

The production of fibroid chips can be avoided if grade 0 fibroids are removed en bloc by cutting through the basal attachment to the uterine side wall with miniature bipolar electrodes such as Versapoint® bipolar electrosurgical system (Gynecare™; Ethicon Inc., New Jersey, USA). These electrodes can be passed down the operating channel of a standard continuous flow operating hysteroscope, and detachment of the grade 0 fibroid can be rapidly achieved. However, given the shape and small size of the electrode, they are not generally suitable for fundally located lesions. Moreover, blind removal of the fibrous specimen from the uterine cavity is not always possible. In these cases, the fibroid will often be left in situ and subsequently degenerate and pass.

Another alternative to reduce the production of fibroid chips is the vaporization electrode. The first vaporizing electrode developed by CIRCON ACMI was the VaporTrode® Grooved Bar. Using the Grooved VaporTrode® and higher wattage, the device is able to vaporize tissue in contact with the electrode (Brooks 1995).

6.4.2 Tissue Removal Systems

Hysteroscopic tissue removal systems appear to have overcome the most frustrating problem with resectoscopes by avoiding the generation of tissue chips. This makes fibroid removal easier to learn than traditional electrosurgical resections (van Dongen et al. 2008). Tissue removal systems use a simultaneous mechanical cutting and tissue retrieval set up that maintains better views while operating. The tissue removal systems consist of a bespoke operating 0° hysteroscope with an operating channel through which a disposable cutting hand piece comprising two rotating hollow metal tubes with a small aperture distally. This is attached to an external suction tubing. A generator provides the electrical energy to rotate the mechanical tissue removal system.

Before the device is inserted, it is important to make sure the window lock is closed when it is not activated. Once the fibroid requiring removal is identified, the window should be aimed toward the top of the fibroid, and the tissue will be sucked inside the window and shaved. As with electrosurgical resectoscopes, the strategy for fibroid removal using these systems is to start on the periphery and move closer to the myometrium. The technique is to position the opening near the pathology, which is then sucked into the opening. Rotation of the inner metal tube then shaves away the pathology. Afterward, the pathology is sucked through the device and trapped in a tissue collector. Gentle pressure is applied with minimal movement of the hysteroscope to ensure the base of the fibroid is removed. To prevent blood and debris obscuring the visual field, it is important to keep the device activated to ensure these products

will be sucked into the window. The first of these systems was the TRUCLEAR™ (Smith & Nephew, Andover, MA) which has been followed by a similar product by Hologic (Bedford, MA, USA) called Myosure™ and Karl Storz (Tuttlingen, USA) called Integrated Bigatti Shaver (IBS). More recently the SYMPHION™ (Boston Scientific, Natick, MA) has been produced which combines a tissue removal system with bipolar radio-frequency energy.

7 Hysteroscopic Polypectomy

7.1 Endometrial Polyps

Endometrial polyps are benign overgrowths of endometrium that project into the uterine cavity. Generally they are pedunculated and are attached to the uterus by an elongated pedicle, but sometimes they are sessile and have a large flat base (Fig. 4).

They can be distinguished from submucous fibroids because they are soft and can be indented by the hysteroscope, and they move with the distension media. They often have a pink-red appearance similar to endometrium, but less vascular polyps can appear pale-gray. The specific hysteroscopic appearance of polyps will vary according to the relative make up of stroma, glands, and blood vessels. Endometrial polyps are common with a prevalence of around 10% in women undergoing a diagnostic hysteroscopy (Clark and Gupta 2005). Most gynecologists recommend the removal of endometrial polyps because of their association with malignant and premalignant conditions (van Dijk et al. 2012; Timmermans et al. 2008). The incidence of polyps and risk of malignancy increases with age.

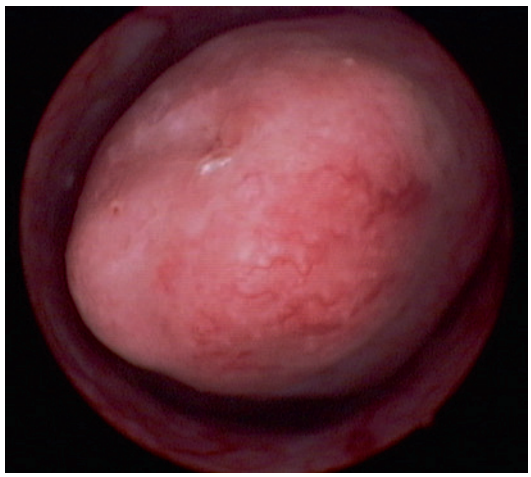

Fig. 4 Endometrial polyp as seen at hysteroscopy

Hysteroscopic visualization allows a subjective assessment of the nature of polyps, but it can also be used to direct biopsies to increase diagnostic accuracy (Birinyi et al. 2004). Indeed, hysteroscopy has the added advantage of allowing simultaneous treatment of detected endometrial polyps. Depending on the local resources and expertise that is available, polypectomy can invariably be performed in the office setting without general anesthesia (Cooper et al. 2015). Hysteroscopic techniques utilizing both miniature mechanical and electrosurgical technologies allow polyp removal under direct vision reducing the risk of incomplete removal and uterine trauma. This represents a shift in management because until recently polyps were often removed blindly using dilation and curettage (D&C) or using large diameter electrosurgical resecting loops under general anesthesia.

7.2 Hysteroscopic Equipment for Removal of Polyps

Hysteroscopic polypectomy began with a range of mechanical instruments that could be passed down the operating channel of the hysteroscope including graspers, biopsy cups, and scissors (Bettocchi et al. 2004; Nathani and Clark 2006; Timmermans and Veersema 2005). However, these instruments are flimsy, making it difficult to remove large pathology, and there have been some studies showing problems with bleeding (Clark and Gupta 2005; Garuti et al. 2008). The resectoscope was the first electrosurgical instrument described for removing endometrial polyps, but these are large diameter instruments necessitating the use of general anesthesia and potentially traumatic, blind cervical dilatation. It is well recognized that polyps are softer than fibroids such

that newer miniature electrosurgical instrumentation such as bipolar electrodes [e.g., Versapoint™ bipolar electrosurgical system (Gynecare, Ethicon, Somerville, NJ, USA)] and monopolar snares have been developed that obviate the need for large diameter hysteroscopes and blind cervical dilatation.

The bipolar electrodes have been demonstrated in observational series to be feasible and safe (Clark et al. 2002a; Kung et al. 1999; Vilos 1999) and have snares. The latter technology is less widely used (Timmermans and Veersema 2005). The previously mentioned hysteroscopic morcellator devices or tissue removal systems, TRUCLEAR™ (Smith & Nephew™, Andover, MA, USA) and Myosure™ (Hologic™, Marlborough, MA USA), are utilized for polypectomy as well as myomectomy. Randomized trials have shown that when compared to electrosurgical devices, tissue removal systems which allow simultaneous tissue cutting and retrieval are quicker to learn, less painful, more acceptable, faster, and more likely to completely remove polyps (van Dongen et al. 2008; Smith et al. 2014a).

7.3 Technique

7.3.1 Electrosurgery

Resecting Loops

The main drawback to the use of large diameter resectoscopes is the need for cervical dilatation and regional or general anesthesia. As with resecting submucous fibroids, the loop is extended beyond the focal lesion and then is activated and drawn toward the operator by closing the loop using the trigger or moving the whole resectoscope or a combination of both methods. The softer, less vascular nature of endometrial polyps in comparison to submucous fibroids makes them much easier to remove. They are rapidly resected either in pieces after a few passes off the resecting loop or en bloc with a sweep of the resecting loop at the polyp base where it attached to the uterine side wall. Occasionally, the inactivated loop can be deployed as a simple snare, closing the extended loop to mechanically detach the polyp from its attachment. Retrieval from the already dilated cervical canal of compressible, glandular polyps is usually achieved under vision by trapping the tissue within the withdrawn loop and end of the hysteroscope and removing the whole unit along the cervical canal.

Bipolar Electrical Resection with Miniature Electrodes

The cutting point of the bipolar electrode works by vaporization. High-temperature Ohmic heating in the immediate vicinity of the active electrode boils the saline to create a vapor pocket. This has the advantage of minimizing bleeding by cauterization of blood vessels. The initial bipolar miniature electrodes were the Versapoint™ electrodes (Fig. 5) that were designed to be used with a bespoke small-diameter operating hysteroscope. This "Versascope™," subsequently modified and renamed the "Alphascope™," is a small-diameter 0° semirigid hysteroscope incorporating a rotating cuff to manipulate the orientation of the bipolar electrodes and other ancillary instruments which have been passed down the expandable disposable outer sheath. The bipolar electrodes can, however, fit down any standard continuous flow operating 30° hysteroscope incorporating a

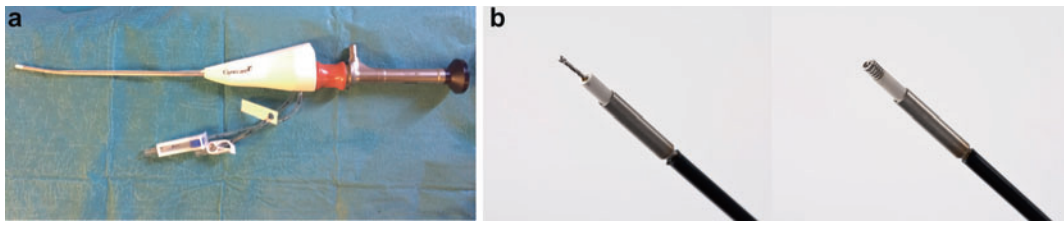

Fig. 5 Alphascope™ and Versapoint™ bipolar electrodes (**a**) twizzle electrode; (**b**) spring electrode

1.6 mm operating channel, making them highly versatile instruments. In contrast to the formal resectoscopes, use of smaller diameter electrosurgical operating set ups minimizes the need for traumatic cervical dilatation. Indeed, the development of the Versapoint™ electrode as a more effective cutting tool compared with flimsy mechanical graspers and scissors was one of the main technologies to shift polypectomy to an office setting.

Once a polyp has been diagnosed, the bipolar electrode is passed down the operating channel of a standard rigid operating hysteroscope. However, if using the Alphascope with its expandable plastic working channel, it is advisable to insert it into the uterine cavity without the electrode in the operating channel. This is because the Alphascope is narrower without the electrode and the operating channel also acts as the outflow so it is harder to clear the turbid fluid at the beginning of the procedure unless it is empty. However, for selected cases such as fundal polyps, it may be beneficial to insert the electrode at the beginning so that the twizzle tip can be bent across the camera lens to create a cutting hook and then allow entry into the uterine cavity. The main drawback of the miniature electrodes is the ability to manipulate them, as the cutting surface is small and fixed in contrast to electrosurgical loops.

When cutting a polyp using an Alphascope, there are three techniques that can be used. The first is to fix the electrode and hysteroscope but swivel the sheath using the rotating cuff creating an arc, which is particularly effective at cutting sidewall polyps. The second is to fix the sheath and hysteroscope and move the electrode in and out. The last technique is to fix the electrode and sheath and then move the hysteroscope and electrode as one instrument. If using the bipolar electrode down a rigid operating 30° hysteroscope, the orientation of the electrode can be altered by moving the light cable and hence the position of the distal offset lens. It is important that with all the techniques, the electrode is not activated when it is going toward the direction of the fundus, as this could lead to perforation and damage. The activated electrode should be withdrawn toward the operator, and when approaching attachments at the fundus and especially the thinner cornual aspects of the uterine side wall, higher magnification is required by ensuring the electrode is close to the distal lens.

The exact technique chosen to cut the polyp will depend on the operator preference, size, and position of the polyp. In the author's opinion, as polyps are compressible and feasible for removal in an office setting, the most efficient technique is to remove the polyp en bloc by cutting its basal attachment to the uterine side wall. This is easiest if the polyps are nonfundal and located on the anterior, posterior, or lateral sidewalls. Sometimes it may be necessary to bisect the polyps if they are large and located fundally so as to access the base. Other operators prefer to cut the polyp into segments, but this is time-consuming and either creates chips of tissue, which may obscure visualization within the cavity or repeated insertions and withdrawal of the hysteroscope. Removing the polyp in one piece avoids these problems, but the larger tissue specimen is harder to remove along the narrow cervical canal.

A variety of biopsy cups, grasping forceps, and snares are available that can be passed down the operating channel to remove the polyp fragments from the cavity. Leaving a small attachment between the polyp and the sidewall will make it easier to grab and stop it swirling around from the inflow of saline. If the polyp is completely detached, then turning off the fluid inflow and gently pushing the polyp using the opened forceps to pin it against the fundus can be used to then take a substantial "bite" of tissue. Others prefer to use inactivated snares to grasp the specimen. To give the greatest chance of traversing the cervical canal without the polyp becoming detached, a good degree of purchase on the polyp by having it firmly grasped should be ensured, and the largest part of the polyp should be brought proximally over the distal lens and then the whole unit moved slowly move backward down the endocervical canal. If this does not work because the polyps are large and fibrous or the cervical canal is narrow, then it may be necessary to break the polyp up under vision although this is rarely possible given its mobility within the cavity. More often the cervix will need to be dilated up to H6–8 and

the hysteroscope and graspers inserted again. Blind retrieval using large polyp forceps should be avoided where possible.

7.3.2 Mechanical

Scissors and Grasping Forceps

Cold scissor resection can be performed using similar equipment as above to detach endometrial polyps. Scissors have the advantage of not producing bubbles that can impede the visual field, and they are also reusable. However, they are fragile, become blunt over time, and are difficult to manipulate. In contrast to the bipolar electrodes, they create bleeding and cannot cut through more fibrous polyps.

Tissue Removal Systems

The TRUCLEAR™ and Myosure™ tissue removal systems have been described in the preceding section on submucous fibroids (Figs. 6 and 7). These technologies can be used for removing uterine polyps. However, in contrast to submucous fibroids, the softer tissue constituting polyps makes them amenable to morcellation using systems with less cutting power (Myosure REACH, LITE & CLASSIC). In the case of TRUCLEAR, a much smaller diameter system is available, the OD TRUCLEAR system with a 2.9 mm rotary cutting blade. The outer diameter is 5.6 mm, and it is a continuous flow system aiding visualization even in the presence of significant tissue debris and bleeding. If the outflow sheath is removed, outflow is then provided by the negative pressure, which draws saline through the aperture and along the hollow activated device. The outer diameter is then reduced to 5 mm, which is advantageous in the office setting, and vaginoscopy is more feasible.

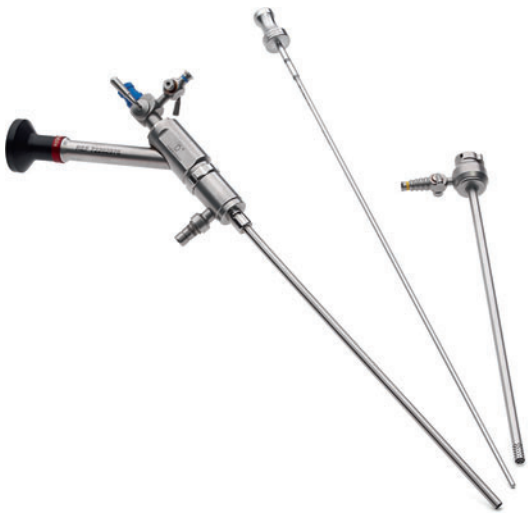

Fig. 6 TRUCLEAR® hysteroscopic tissue retrieval system

The technique for morcellation is similar to removing fibroids. The distal aperture incorporating the cutting edges of the rotating inner and outer hollow tubes should be embedded in the polyp tissue and not visible. As polyps are mobile in a fluid distension media, they will be seen to move when the device is in contact with the tissue, simultaneously cutting and aspirating material. Movement of the device should be kept to a minimum. Small rotations of the hand piece to redirect the cutting window are all that is generally required. As the polyp base is reached, more exaggerated vertical or horizontal movements of the hand piece will lever the cutting window up against the uterine side wall. The ease of use of these systems and short learning curve compared to traditional resectoscopy was highlighted in a recent randomized control trial (RCT) (van Dongen et al. 2008). A recent RCT showed that the TRUCLEAR tissue removal system was quicker, less painful, and more acceptable and successful compared with Versapoint™ electrosurgery for the office removal of endometrial polyps (Smith et al. 2014b).

8 Endometrial Destruction for Abnormal Uterine Bleeding

8.1 Endometrial Destruction

Heavy menstrual bleeding is one of the commonest reasons patient consult with their gynecologist. There is an increasing range of medical therapies, but most have a hormonal basis for action. Some women do not like taking hormones long term, while others suffer from side effects, and these problems can limit the application of medical therapies. Traditionally, after medical

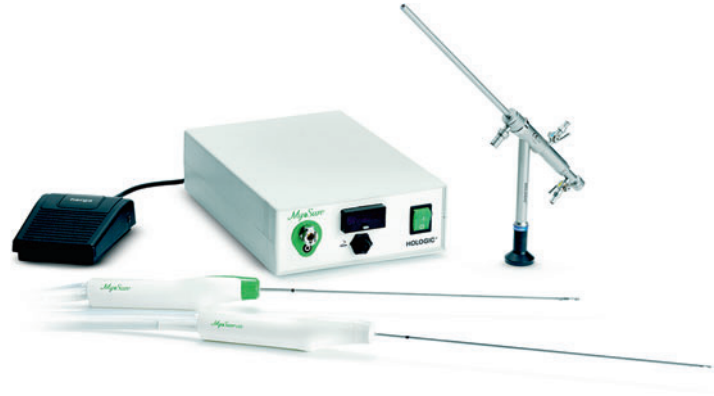

Fig. 7 Myosure® hysteroscopic tissue retrieval system

Fig. 8 The NovaSure radio-frequency ablation system (an example of a semiautomated, global, second-generation endometrial ablation device)

therapies had failed, definitive treatment with hysterectomy was used, but this has the morbidity and mortality associated with a major surgery. Moreover, patient preference studies have shown that women put a high value avoiding hysterectomy and retaining their uterus. Endometrial destruction techniques, i.e., ablation and resection of the endometrium, provide a cheaper, safer alternative to hysterectomy. The first-generation hysteroscopic techniques include laser ablation, rollerball ablation, and transcervical resection of the endometrium (TCRE). The costs of laser equipment were prohibitive so that electrosurgical resection with cutting loops and/or rollerball ablation using roller ball electrodes became the preeminent technique. When comparing TCRE to with rollerball ablation, there is no evidence of difference in rates of complication or re-intervention (Lethaby et al. 2005).

The second-generation techniques were then developed. These semiautomated technologies utilized the principle of controlled, global thermal destruction of the endometrium but without the requirement for enhanced operative hysteroscopic skills. They also aimed to reduce complications, particularly those of uterine trauma and fluid overload. While evidence supports their enhanced feasibility and safety, they are generally less flexible being restricted to use in regular-shaped cavities without submucous fibroids or congenital anomalies. There have been many different devices that have come to market with some no longer in use. The most prevalent devices are based upon the application to the endometrial surface of impedance-controlled radio-frequency energy (NovaSure™ Fig. 8) or conducted heat from fluid within a pressurized balloon [Thermachoice™ (Gynecare™; Ethicon™ Inc., NJ, USA); Cavaterm™(Wallsten Medical SA, Lausanne, Switzerland); Thermablate™ (Gynecare^{tm}, NJ , USA)]. The Genesys HTA™(Boston Scientific) is a hydrothermal ablation method that uses heated saline and allows for visualization of the endometrial cavity during the ablation procedure. It allows for ablation of larger and irregularly shaped endometrial cavities.

The main drawback of uterine sparing endometrial ablation in comparison to hysterectomy is that it cannot guarantee amenorrhea. Around 10% of patients who have endometrial ablation will go on to have a further intervention usually in the form of a hysterectomy (Peeters et al. 2013; Smith et al. 2014a). Research looking at prognostic factors have found that large uterine cavities (>9 cm), preoperative dysmenorrhea, and younger age (<45 years) are associated with a higher chance of failure (El-Nashar et al. 2009). The reasons for hysterectomy are not always confined to persistent or recurrent abnormal uterine bleeding as some women develop cyclical pain thought to be a result of iatrogenic adenomyosis or hematometra.

8.2 Equipment

8.3 Technique of Transcervical Resection of the Endometrium and Endometrial Electrocoagulation

The first-generation techniques are all done under hysteroscopic vision. This has the advantage of allowing treatment in the presence of small fibroids, endometrial polyps, uterine abnormalities, or a large cavity. Unfortunately, these techniques require more time and higher skill levels and use distension media that can lead to complications of fluid overload and electrolyte imbalances.

The technique used for transcervical resection of the endometrium (TCRE) is similar to that used for fibroid resection, while endometrial electrocoagulation makes use of a rollerball electrode instead of a loop electrode. The rollerball electrode is easier to learn and does not generate tissue chips. The rollerball cannot be used to simultaneously treat other causes of heavy menstrual bleeding such as fibroids and requires the endometrium to be thin.

It is important to visualize all the landmarks before starting, and it can also be useful to mark the point near the endocervix that you wish to resect or ablate before starting. This is because when the activated electrode is drawn toward the surgeon, it is easy to go beyond the area you wish to resect/ablate. It is important to take a systematic approach to treatment of the cavity. The cornual and fundal areas are technically the most difficult areas to treat and are resected by moving the entire hysteroscope using a forward-facing loop or rollerball. Drawing the activated electrode toward the surgeon treats the anterior and posterior walls by either moving the entire hysteroscope or closing the electrode or a combination of these two movements.

The complications of TCRE are similar to fibroid resection. The most serious complication is uterine perforation. This can be minimized by using the rollerball particularly in the cornual and fundal areas. Other serious complications include fluid overload, primary hemorrhage, and gas embolism from the bubbles produced by the electrode entering an open vessel. An important cause for treatment failure is a hematometra. It usually presents as cyclical menstrual pain after TCRE. The diagnosis is made when ultrasound or MRI shows a fluid-filled cavity. Treatment is with either hysterectomy or cervical dilatation and drainage. If drainage is attempted, then this may need to be done under ultrasound guidance due to the dense intrauterine adhesions that can form after resection.

8.4 Technique for Second-Generation Endometrial Ablation

Rates of satisfaction are consistently high for second-generation techniques, and they are now an established alternative to hysterectomy. The three most commonly used second-generation devices reported in the literature utilize energy applied via thermal balloons, bipolar radiofrequency electricity, and microwave energy. A network meta-analysis showed that bipolar radio frequency and microwave ablative devices are

more effective than thermal balloon and free-fluid ablation in the treatment of heavy menstrual bleeding in terms of inducing amenorrhea (Daniels et al. 2012). However, while a new small microwave device has been introduced (Minitouch™), these data relate to the original larger diameter Microsulis™ system that has now been taken off the market for commercial rather than clinical reasons. Longer-term data comparing bipolar radio frequency and thermal balloon devices have shown no difference in re-intervention rates or health-related quality of life (Kleijn et al. 2008; Smith et al. 2014a). Table 1 summarizes the types and features of currently available ablative technologies.

9 Hysteroscopic Treatment of Acquired Uterine Abnormalities

9.1 Intrauterine Adhesions

Intrauterine adhesions are defined by scar tissue between the uterine walls. This is also called Asherman's syndrome. It was thought that it occurred following excessively vigorous curettage of the endometrium in a recently pregnant or pregnant uterus. However, it can occur after an infection of the uterus or uterine surgery. Patients rarely present with cyclical pain due to trapped menses but more commonly with amenorrhea and infertility. Hysteroscopy is the gold standard for accurate diagnosis and assessment of intrauterine adhesions. A hysterosalpingogram can also be screening test and has the advantage of being

Table 1 Description of currently available second-generation endometrial ablation devices and outcome data

Device	Mode of action	Source of information	Treatment duration	Heavy bleeding rate (%)	Amenorrhea rates (1 year) (%)	Satisfaction rates (1 year) (%)
Electrical						
NovaSure	Fan-shaped bipolar radio-frequency electrode	(Smith et al. 2014a)	90 s	8	56	93
Thermal balloon						
Thermablate	Balloon with heated glycine	(Penninx et al. 2016)	128 s	21	23	69
Cavaterm	Balloon with heated glycine	(Brun et al. 2006; Hawe et al. 2003)	10 min	3–7	33–36	81–93
Free-flowing saline						
Hydrothermablation	A closed system is formed with the cavity to deliver heated saline directly to the endometrium	(Corson 2001; Penninx et al. 2011)	10 min	14–18	24–38	79
Microwave						
Minitouch	Microwave energy via an induction loop placed in the uterine cavity	(Tas and Van Herendael 2014)	60 s	Not available	84	Not available

Table 2 Classification system for intrauterine adhesions

Mild	Filmy adhesions composed of basal endometrium, producing partial or complete uterine cavity occlusion
Moderate	Fibromuscular adhesions that are characteristically thick and still covered by endometrium. They may bleed on division, partially or totally
Severe	Composed of connective tissue with no endometrial lining and likely to bleed upon division, partially or totally occluding the uterine cavity

able to assess tubal patency in patients with infertility problems.

The type and extent of intrauterine adhesions have been classified according to Valle and Sciarra (Table 2). Other classification systems such as the American Fertility Society classification exist (Valle and Sciarra 1988).

9.2 Technique

Various different techniques can be employed to restore the size and shape of the uterine cavity. Where there are filmy adhesions only, balloon distension and insertion of intrauterine contraceptive devices have been described as non-hysteroscopic techniques. Hysteroscopic techniques have the advantage of being performed under direct vision, and various methods have been employed depending on the severity of the intrauterine adhesions. These include blunt or sharp adhesiolysis, using mechanical methods, laser instrument, and electrosurgical instruments. Simple distension of the uterine cavity during diagnostic hysteroscopy has also been described for adhesiolysis of filmy adhesions.

In some patients, landmarks remain obscure and entry into the uterus may not be possible. In these patients, it is necessary to perform simultaneous laparoscopy, fluoroscopy, or ultrasound to reduce the risk of perforation. Ultrasound is more useful for patients with lower segment scarring that have a normal upper segment. With laparoscopic guidance, the light source of the laparoscope is reduced so that the light from the hysteroscope can be observed through the uterus to locate its position and minimize the risk of uterine perforation. A uniform glow of the uterus is reassuring, while focused light indicates impending perforation. With complex cases, the risk of intravasation of the distension media is increased so, as with all operative hysteroscopy, careful fluid balance monitoring is required.

Increased uterine cavity size can be achieved by myometrial scoring with scissors or a Colling's knife electrode. Drawing the resectoscope from the fundus toward the isthmus with the knife electrode continuously activated makes the myometrial incisions. The Colling's knife electrode is used at a power setting of 100 W at pure cutting current. This is repeated around eight times so that equally spaced incisions are made around the complete radius of the uterine cavity and it opens up like an accordion. Myometrial scoring has also been described using miniature bipolar electrodes in an attempt to increase the capacity of a hypoplastic or T-shaped uterus (Di Spiezio Sardo et al. 2015).

Various postoperative interventions have been described to try and reduce the likelihood of recurrence of adhesions. Insertion of inert intrauterine devices or Foley balloon catheters has been used in an attempt to help maintain separation of the uterine walls. Postoperative estrogen therapy is thought to promote endometrial overgrowth and re-epithelialization of the scarred surface. Steroids have been advocated to reduce the inflammatory response as well as antibiotics to prevent endometritis. Repeated postoperative office hysteroscopy with mechanical lysis of new, filmy adhesions, prior to them becoming fibrous, until no new adhesions form has recently been reported (Yang et al. 2016).

9.3 Retained Products of Conception

Chronically retained products of conception (RPOC) or placental remnants can occur after miscarriage, termination of pregnancy, vaginal deliveries, and cesarean deliveries. Retained

products of conception can be associated with short-term problems such as infection, abdominal pain, and uterine bleeding. Long-term problems include the formation of intrauterine adhesions. The most common treatment for RPOC is dilation with suction, blunt, or sharp curettage. However, for RPOC beyond 6 weeks' duration, hysteroscopic alternatives are emerging which facilitate focused and complete removal under direct vision, potentially reducing the risk of uterine trauma and intrauterine adhesions.

9.4 Technique

The techniques described include use of a cold (inactivated) resection loop to mechanically remove RPOC by entrapment of tissue between the loop, and the hysteroscope and repeated removal and insertion of the resectoscope until the cavity is empty. The use of tissue removal systems to selectively remove tissue under direct vision has been reported and seems well suited to this task as electrosurgical energy is not needed and tissue can be simultaneously cut away and extracted avoiding repeated insertion and removal of the hysteroscope (Hamerlynck et al. 2013; Smorgick et al. 2014). There is a lack of evidence to suggest that the hysteroscopic technique is superior to blind surgical evacuation at the moment. Nevertheless, in selected cases such as previous failed surgery or where there are known structural abnormalities, the hysteroscopic approach may be appropriate. Research is required to help guide best practice.

10 Hysteroscopic Treatment of Congenital Uterine Anomalies

10.1 Uterine Septum

Hysteroscopic septoplasty describes the resection of an intrauterine septum that is a Müllerian duct anomaly. The uterus and fallopian tubes are formed as the paramesonephric ducts fuse caudally in early embryonic life forming the fallopian tubes, uterine cavity, and upper third of the vagina. During the fusion of the paramesonephric ducts, a septum is formed in the uterine cavity that is usually reabsorbed by 20 weeks of gestation. Failure of the reabsorption process results in a septate uterus, which can be either partial or complete and in severe cases can extend to involve the cervix and the top of the vagina. This can be distinguished from a bicornuate uterus, in which there is failure of the fusion of the paramesonephric ducts, because there is no effect on the uterine body.

Hysteroscopic resection of the intrauterine septum has superseded conventional abdominal approaches to metroplasty that included the John's or Tompkin's technique. Not only do hysteroscopic procedures reduce the morbidity compared to the abdominal approach, but they also produce superior reproductive outcomes. Because the integrity of the uterine cavity is not breeched, hysteroscopic procedures avoid the risks of uterine rupture during labor.

10.2 Technique

The principle of septoplasty is to divide the septum along the midpoint rather than excise the septum. The tissue is usually fibroelastic, so does not bleed. Division can be done using electrosurgery using either the Versapoint™ electrode or resectoscopic division using a Colling's knife electrode. Mechanical division can be achieved using scissors. Electrosurgical and mechanical techniques can be combined. More rarely laser such as Nd:YAG can be used. Whichever technique is used, the operator has to take special care to determine the depth and direction of cutting, especially as the division of the septum often requires hysteroscopic movements toward the fundus that increase the risk of perforation. To try and reduce the risk of the perforation, the operator should not aim to create a cavity that is arcuate. Depth of cutting can be further assessed with either simultaneous ultrasound or laparoscopy. With laparoscopy, the intensity of the light

Fig. 9 Essure™ micro-insert

source is reduced so that the intensity of light from the hysteroscope can be monitored. If the uterus glows in a uniform manner, it is presumed that the risk of perforation is low. Laparoscopy also has the advantage of keeping bowel away from the uterus but is not as accurate as ultrasound for assessing the depth of myometrium. However, if preoperative radiological imaging with either 2D/3D ultrasound or MRI clearly distinguishes a septate uterus from a bicornuate uterus, then a purely hysteroscopic approach is feasible. The operator should look out for soft, trabeculated, pink myometrial tissue as opposed to the pale, smooth, fibroelastic septal tissue to ascertain when the limits of the septum in relation to the uterine fundus has been reached. Bleeding is not a reliable indicator of reaching myometrial tissue as the high inflow pressures of distending media may tamponade such bleeding. If both cornual recesses can be visualized with the hysteroscope at the level of the internal os and the sound length is at least 7 cm, then an adequate uterine cavity has been restored following septoplasty.

Hysteroscopic metroplasty to restore the shape of the hypoplastic or "T"-shaped uterus has been reported by scoring the myometrium with activated miniature bipolar electrodes in an attempt to increase the uterine capacity (Di Spiezio Sardo et al. 2015). The electrodes can also be used to create outflow channels in non-communicating rudimentary uterine horns with the aid of ultrasound or laparoscopic guidance. Foley catheters can then be hysteroscopically placed to allow fistulization to occur creating permanent outflow tract.

11 Hysteroscopic Sterilization

Since the introduction of hysteroscopic sterilization, it has steadily increased in popularity, although more recently the US Food and Drug Administration (FDA) has required the device manufacturer, Bayer, to conduct a post-marketing surveillance study to compare adverse events with Essure™ with those seen with tubal ligation due to complaints from some patients and recent re-intervention data (Mao et al. 2015). The benefits of hysteroscopic sterilization are that it avoids the abdominal route, it allows a quicker return to normal activities, and it can be performed without general anesthesia. These advantages make hysteroscopic sterilization a good option for women who want to avoid, or have contraindications, general anesthesia and abdominal surgery. The most commonly applied technique is Essure™, which involves the placement of a 4 cm expanding spring into the fallopian tubes (Fig. 9). New warnings must be printed on the labels of the implantable sterilization device Essure™ after reports of serious side effects.

The reported rates of successful bilateral placement vary between 81% and 98% with higher success rates in studies published since 2007 (la Chapelle et al. 2015). Following successful bilateral placement, confirmation of correct placement rates is between 90% and 100% (la Chapelle et al. 2015). Hysteroscopic sterilization with the Essure™ system is an effective method of contraception. In a case series of 4306 procedures, a total of seven women (0.16%) became pregnant. Of these seven, three ignored advice to refrain from intercourse before assessment for satisfactory placement, bringing the pregnancy rate after establishing correct placement to 0.09% (Povedano et al. 2012).

Reported serious complications are rare, and in the largest series reported to date of over 4000 procedures, the most common adverse event was vasovagal reaction, which occurred in around 2% of cases. Expulsion of the micro-insert occurred in 0.4% of women, although this occurred before the 3-month follow-up in most cases. In three cases,

the micro-inserts were erroneously placed in the myometrium (0.06%), and in two other cases, there was asymptomatic migration into the abdominal cavity (0.04%). The migrated devices were left in the abdominal cavity. There were also two cases of pelvic inflammatory disease (0.02%). Longer-term complications included two allergies to nickel (0.04%) and one woman who had persistent abdominal pain (0.02%) (Povedano et al. 2012). Because the incidence of nickel allergy is so low, it has been removed as contraindication to placement. Nevertheless, it is good practice to tell patients that the micro-inserts do contain small amounts of nickel, but it is unlikely to be clinically significant. It is more difficult to treat longer-term complications which often require coil removal via an abdominal route. This can be complicated because the micro-insert may be lodged in surrounding structures and can conduct electrical energy making removal difficult.

A recent US cohort study compared 8048 patients undergoing hysteroscopic sterilization with over 40,000 undergoing laparoscopic sterilization between 2005 and 2013, and they found, at 1 year after surgery, the risk of unintended pregnancy was around 1% and comparable between techniques. However, around 1 in 50 women undergoing hysteroscopic sterilization required reoperation to complete, reverse, or rectify complications arising from the procedure compared with 1 in 500 women undergoing laparoscopic sterilization (Mao et al. 2015). While the convenience of office-based hysteroscopic sterilization will be attractive to many women, they also need to be informed of the reoperation data to help them decide which sterilization procedure is most appropriate for them.

11.1 Equipment

11.2 Essure Technique

Prior to the procedure, nonsteroidal anti-inflammatory drugs (NSAIDs) are given to reduce tubal spasm, although evidence for this practice is not strong (Chern and Siow 2005; Nichols et al. 2006). There is no need to routinely give antibiotics during hysteroscopic sterilization.

The introducer provided is inserted to prevent retrograde leakage of distension fluid along the working channel into the working channel of the hysteroscope, which is then inserted through the cervical canal under direct vision to access the uterine cavity. This can usually be achieved vaginoscopically without the need for vaginal instrumentation or local anesthesia unless the woman is nulliparous or undergone cesarean sections or cone biopsies of the cervix. Both tubal ostia need to be visualized before beginning the procedure. This is best done by gently rotating the hysteroscope to allow the offset lens to look in each lateral direction.

The first micro-insert delivery catheter is then fed along the working channel and the offset lens of the hysteroscope closely aligned with the selected tubal ostia (Fig. 10). Close proximity of the distal hysteroscope to the tubal ostia aids

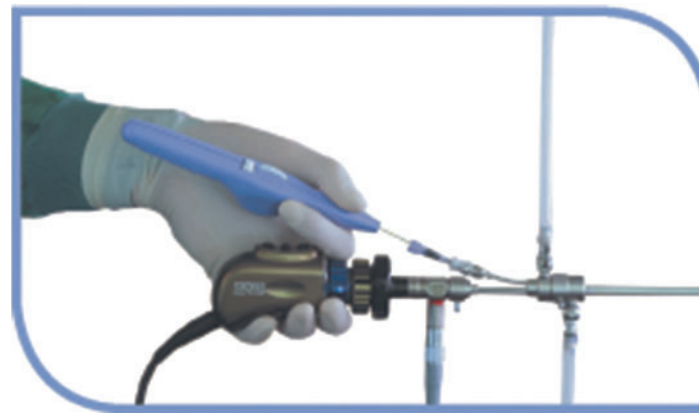

Fig. 10 Essure™ hysteroscopic system of sterilization; with the help of an introducer, the Essure catheter goes down the operating channel of a hysteroscope to allow deployment of the Essure insert in the fallopian tube

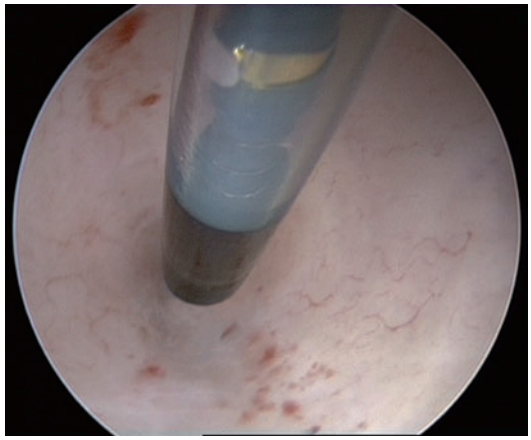

Fig. 11 Placement of the Essure™ micro-insert into the tubal ostia; the catheter tip is advanced into the fallopian tube until the black marker reaches the ostia

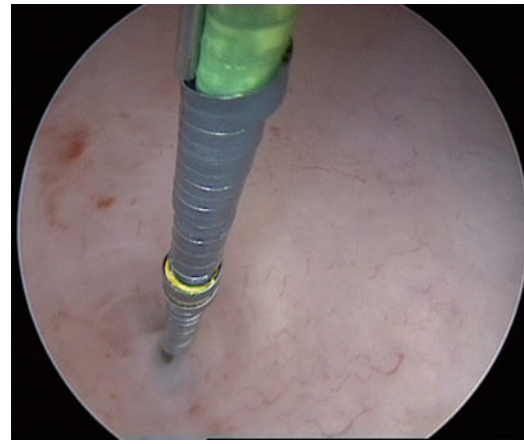

Fig. 12 Placement of the Essure™ micro-insert into the tubal ostia; the catheter is retracted, and the black positioning marker disappears. The gold band must be located just outside the ostium before the insert is detached

precise passage of the device minimizing the risk of tubal spasm. The rigid hysteroscope can also act to splint the fragile micro-insert, preventing it bending if tubal resistance is encountered. With gentle forward movements, the micro-insert is passed into and along the tube until the black positioning marker on the insertion catheter is flush with the ostia (Fig. 11). The surgeon or assistant then retracts the outer catheter by rotating the thumbwheel until it will no longer rotate. Using careful movements, the gold marker on the micro-insert should then be aligned just outside of the tubal ostia (Fig. 12). Pressing the button on the handle deploys the micro-insert. Rotating the thumbwheel again until it will no longer rotate retracts the inner catheter. Ideally three to eight expanded coils should be seen in the uterine cavity (Fig. 13).

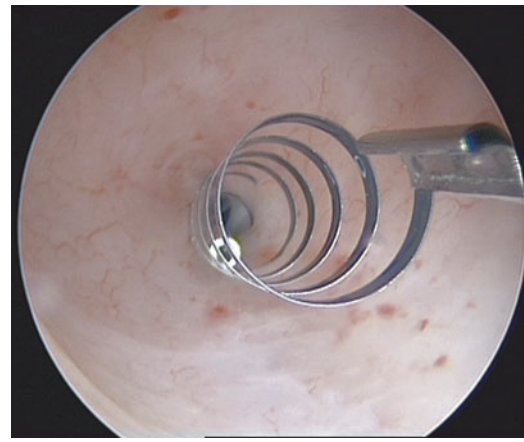

Fig. 13 Placement of the Essure™ micro-insert into the tubal ostia; the catheter tip is advanced into the fallopian tube until the black marker reaches the ostia. Once the catheter is withdrawn, three to eight coils should be seen outside the ostium

11.3 Confirmation of Correct Placement

The main disadvantage of hysteroscopic sterilization compared to laparoscopic sterilization is that it is not immediately effective; at least 3 months is required before tubal fibrosis and occlusion occur for the procedure to be effective. During this time, the woman needs to use alternative forms of contraception. After 3 months, post-procedure imaging is required to check for placement and occlusion. In the USA, the FDA requires a hysterosalpingogram for all patients with Essure™ sterilization to confirm tubal occlusion. In Europe, X-ray and transvaginal ultrasound are accepted, less invasive alternative radiological confirmation tests to confirm satisfactory device placement. Confirmation of the correct location has been reported to correlate well with effectiveness (Veersema et al. 2005).

12 Hysteroscopic Tubal Occlusion for the Treatment of Hydrosalpinges

Essure can be considered in women who require tubal occlusion prior to in vitro fertilization (IVF) as treatment for hydrosalpinges. Although there may be some concern regarding the effect of a foreign body on embryo implantation, there appears to be tissue encapsulation of the device after implantation. Several small studies have reported pregnancies from IVF following sterilization with Essure. A retrospective review of all pregnancies reported after Essure in situ in the Netherlands, including unintentional (failed Essure procedures) and those that were intentional, resulting from off-label use of Essure micro-inserts for hydrosalpinx closure before in vitro fertilization, intracytoplasmic sperm injection with embryo transfer, or in vitro fertilization with embryo transfer after regret of sterilization (Veersema et al. 2014). Of the 8 unintended pregnancies and 18 intended pregnancies, all resulted in birth of a full-term healthy baby. So it appears unlikely that the presence of intratubal micro-inserts interferes with implantation and the developing amniotic sac and fetus.

12.1 Technique

The technique is as described previously for Essure hysteroscopic sterilization. Some operators advocate more distal placement of the micro-inserts so that no more than three trailing coils are within the uterine cavity. In the presence of a unilateral hydrosalpinx, a single device placement only is required.

13 Hysteroscopic Tubal Cannulation

Tubal catheterization is a technique used to treat a proximal fallopian tube blockage (PTB) diagnosed following hysterosalpingogram (HSG). It is thought that the narrow and thick, less ciliated proximal segment of the fallopian tube is particularly prone to obstruction, initially by material that can flow back from the uterus, and then in the luteal phase of the cycle by secretions produced locally. As PTB generally occurs in otherwise undamaged tubes, tubal catheterization can potentially successfully re-cannulize the tube.

Data for hysteroscopic treatment of PTB is scarce especially in the ambulatory setting. Tubal catheterization is reported to be successful in approximately 50% of patients (10), and 20–40% of these women have been reported to become pregnant either spontaneously or after ovulation induction or intrauterine insemination (Robinson et al. 2013).

13.1 Equipment

The tubal catheterization system is shown in Fig. 14. The cannula and guidewire fit down the standard 5Fr-working channel of an operating hysteroscope. Procedures can be performed in both the inpatient and outpatient setting.

13.2 Technique for Tubal Cannulation

The radiological procedure of selective salpingography and tubal catheterization has been adapted for use under direct hysteroscopic vision thereby avoiding exposure to ionizing radiation. A 5–5.5 mm 30° continuous flow operative hysteroscope is inserted. A fine catheter is passed down the 5-7Fr working channel of the hysteroscope and guided toward the tubal ostium. The catheter is pushed gently under vision into the tubal ostium and methylene blue dye instilled via a syringe, through the lumen of the catheter. If this does not overcome the obstruction, i.e., the catheter cannot be passed into the tubal ostium or retrograde spill of dye is noted despite forward instillation pressure, a guidewire is railroaded through the lumen of the catheter. The guidewire is pushed gently into the cornual portion of the tube and the instillation of dye repeated.

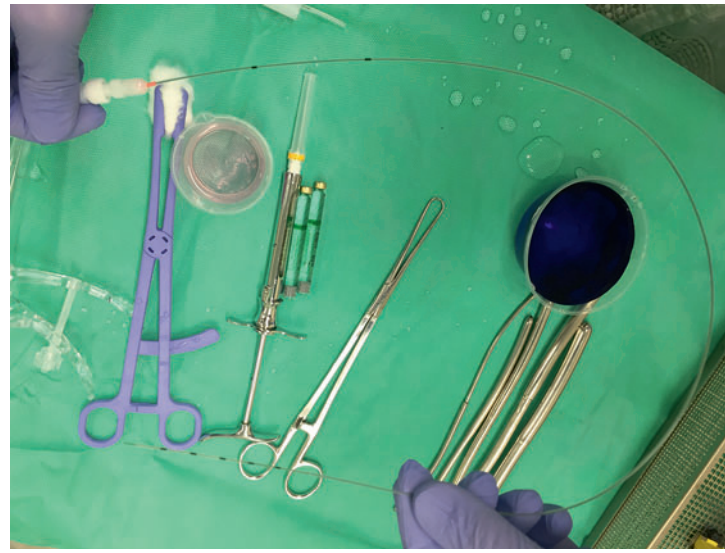

Fig. 14 Tubal catheter system for hysteroscopic tubal cannulation of proximal tubal occlusions

Hysteroscopic tubal cannulation can also be done in theater as a day case under laparoscopic guidance and a dye test performed at the end of the procedure to assess tubal patency. In the ambulatory hysteroscopy setting, confirmation that PTB has been overcome can be inferred by ease of passage dye without retrograde spill, pre- and post-procedure transvaginal pelvic ultrasound (TVS) to look for free fluid within the pelvis, and hysterosalpingo-contrast sonography scanning or follow-up HSG arranged to confirm restoration of tubal patency.

Risks of the procedure include pelvic infection and uterine trauma. Excessive forward pressure must be avoided, especially if using a fine guide wire, as this risks tubal perforation. This complication should be suspected where the patient experiences acute, sharp, localized pain as the serosal surface of the uterus is breached. The risk of tubal perforation during the procedure is approximately 2%.

14 Outpatient Procedures

Initially hysteroscopy was developed as an inpatient procedure, but advances in equipment, in particular the reduction in size of optics, have allowed first diagnostic and now a range of minor operative procedures in the outpatient setting (Clark and Gupta 2005; Clark et al. 2002b, Kremer et al. 2000). Outpatient hysteroscopy, ambulatory hysteroscopy, and office hysteroscopy all describe procedures that are done without general anesthetic and avoid admission to hospital. Women value the convenience of an immediate diagnosis and treatment. Not only is office treatment well-accepted and convenient, but it also has been shown to be more cost effective (Cooper and Clark; Moawad et al. 2014).

14.1 Equipment and Technique

Office hysteroscopy has the potential to perform the following minor hysteroscopic procedures without the need to readmit the patient to hospital:

- Localization and removal of a missed intrauterine contraceptive devices
- Endometrial polypectomy
- Resection of small type 0 submucous fibroid/office preparation of partially intramural myomas (OPPIuM) – mucosal incision
- Minor adhesiolysis (filmy adhesions)
- Endometrial ablation using second-generation devices
- Outpatient sterilization
- Tubal catheterization

The equipment and operative techniques have been provided in the preceding sections. One of the biggest challenges in office hysteroscopy is pain relief. National, evidence-based guidelines have been published for best practice when conducting office hysteroscopy to minimize adverse outcomes and optimize the patient experience (Clark et al. 2011). As with any procedure that involves the instrumentation of the uterus, this can be associated with pain, anxiety, and embarrassment. Thus, in addition to a gentle, atraumatic, proficient, and expeditious surgical approach utilizing small-diameter instrumentation, communication with the patient becomes paramount, and this can be promoted by having a member of staff dedicated to providing reassurance and support in what has been termed the vocal-local. In women without contraindications, analgesia should be taken 1 h before the procedure to reduce postoperative pain. Conscious sedation with inhalational agents such as nitrous oxide may be useful in patients who are very anxious. There is not sufficient evidence to recommend routine use of cervical preparation, but all women who require cervical dilation should receive local anesthetic.

15 Safety of Operative Hysteroscopy

15.1 Complications

All procedures have risks of complications, and hysteroscopic procedures are no exception. There are general risks associated with anesthesia, and there are risks associated with the specific procedure. With hysteroscopic procedures, there are particular risks of inserting and activating electrosurgical, thermal, or mechanical instruments within the uterus, and there are risks associated with the distension media. Insertion of the instruments is often made more difficult because of the cervical dilatation needed to accommodate the larger diameter operating instruments. Intravasation of distension media is also more of a problem due to longer operating times and opening up of deep myometrial vessels during resection of type 1 and 2 submucous fibroids. Other perioperative complications include hemorrhage, cervical trauma, uterine perforation, and electrosurgical burns. Postoperative endometritis or ascending pelvic infection can occur although the routine use of prophylactic antibiotics is not recommended (Van Eyk et al. 2012; Thinkhamrop et al. 2007). Rare late complications can include intrauterine adhesions, uterine rupture, and hematometra after endometrial destruction techniques.

In a prospective multicenter study of 13,600 women looking at complications of hysteroscopic procedures, diagnostic procedures had significantly fewer complications (0.13%) than operative procedures (0.28%). The most common complication for operative procedures was uterine perforation (0.76%). Four cases of perforation resulted in heavy bleeding that required treatment by laparoscopy (n = 2), laparotomy (n = 1), or hysterectomy (n = 1). Fluid overload, defined as the absorption of more than 1500 mL of distension media with clinical consequences for the patient, occurred in 0.2% of operative procedures. Four of the five cases occurred during fibroid resection and one during an endometrial resection. The operative procedure associated with most complications was adhesiolysis, risk of complication 4.5%, compared to the least risky operative procedure polypectomy, risk of complication 0.4% (Jansen et al. 2000).

Using good equipment and attaining surgical proficiency through adequate training and an appropriate caseload in clinical practice as well as considering the potential causes of operative difficulties can minimize complications. Possible causes for common problems during operative hysteroscopy include:

- Difficulty with dilation of cervix – scar tissue, acutely anteverted or retroverted uterus, formation of a false passage
- Poor vision – inadequate distension, out of focus, debris (increase suction, open outflow, clear blocked suction holes)
- Bleeding during hysteroscopy – low distension pressure, inefficient coagulation, cutting too deeply

Table 3 RCOG classification of operative hysteroscopy levels

Level 1	Diagnostic hysteroscopy with target biopsy Removal of simple polyps Removal of intrauterine contraceptive device
Level 2	Proximal fallopian tube cannulation Minor Asherman's syndrome Removal of pedunculated fibroid (type 0) or large polyp
Level 3	Division/resection of uterine septum Major Asherman's syndrome Endometrial resection or ablation Resection of submucous fibroid (type 1 or type 2) Repeat endometrial ablation or resection

- Rapid fluid absorption – high distension pressure, transecting deep myometrial vessels, uterine perforation

15.2 Case Selection

Case selection is important to minimize complications, particularly when learning new techniques. For example, when learning fibroid resection, it is advisable to master the resection of small type 0 or 1 submucous fibroids attached to the uterine sidewalls before moving onto larger, deeper type 2 or fundal fibroids. Theoretically type 2 fibroids can be hysteroscopically resected if they are not transmural. However, there are some cases that even experienced surgeons should not attempt. Although counterintuitive, the highest complication rates were in those surgeons performing >50 procedures. This may be because the more experienced surgeons are doing the most difficult cases, but it also emphasizes the importance of audit and careful consideration before procedures are performed (Jansen et al. 2000).

Not only is it important to consider the complexity of the case but also pain relief and embarrassment with procedures done in the ambulatory setting without anesthesia. Various strategies can be employed to reduce pain, but some patients will find these procedures very embarrassing or painful, and it can be difficult to predict. Important clues can be gained by how the patient has tolerated other uterine procedures such as endometrial biopsies or diagnostic hysteroscopy. If dilation of the cervix is needed, local anesthetic should be used. Analgesia and antiemetics can also be given prior to the procedure. It is important to have a low threshold for stopping the procedure in the ambulatory setting.

16 Teaching

National training bodies, such as the Royal College of Obstetricians and Gynaecologists (RCOG) and American Association of Gynecologic Laparoscopists (AAGL), are providing structured training and accreditation packages for hysteroscopic training. The RCOG has provided a list of procedures stratified by complexity and therefore risk (Table 3).

Operative hysteroscopy skills are difficult to learn, and structured training and mentorship is required for competencies to be achieved. The rapid increase in the number of procedures done while patients are awake along with decreased training hours has led to legal and ethical concerns about training on real patients. Many minimally invasive training programs around the world have tried to tackle this by incorporating training outside the operating room. There are models and computerized simulators that are now available to help performance. However, the application of hysteroscopic models appears to have lagged behind the use of their laparoscopic counterparts. Despite this, a wide variety of models have been used although few of them have been validated. Animal tissues such as pig bladders have been used as "wet" models. Pig bladders can be used to simulate endometrial ablation, and by using stitches, they can also be used to simulate polyp and septum resection (Hiemstra et al. 2008).

Animal hearts have also been used to simulate endometrial ablation and resection. Training on vegetables offers a cheaper and more readily available method. Reports of peppers and squash being used to practice biopsy and tissue removal have been stated (Hiemstra et al. 2008; Kingston et al. 2004).

Training using plastic models or box trainers has been shown to improve resident performance (Burchard et al. 2007). Tactile skills can be improved performing abstract tasks such as removal of pin from the sidewall of plastic uterus, or models with fake pathology for resection have been made (Burchard et al. 2007).

Virtual reality simulators create a safe and controlled environment, but more importantly, they create standardized environments that allow the objective performance of the trainee. The VirtaMed HystSim™ (Hysteroscopic Surgery Simulator System) (Zurich, Switzerland) is the only hysteroscopic simulator available, and it has a large number of stored cases and pathologies with different levels of difficulty. The disadvantage of the simulator is the high cost and the lack of haptic feedback.

17 Clinical Governance and Audit

An important part of clinical governance is risk management. Periodic assessment of infection control, staff training, equipment condition, patient information leaflets, and local protocols should be performed.

Audit is an essential tool to improve and maintain standards especially when setting up new services. Areas suggested for audit include:

- Complications of hysteroscopic surgery (e.g., uterine perforation, fluid overload, infection, vasovagal reactions, heavy bleeding, and cervical trauma)
- Failure rates of operative hysteroscopy
- Standards of documentation
- Use of perioperative and postoperative analgesia
- Patient satisfaction in terms of pain experienced, acceptability, and quality of services

18 Future Developments

In the past, new developments in operative hysteroscopy have been dominated by miniaturization of equipment. With an increasing number of procedures being performed in the office setting, it is likely that future developments will also focus on miniaturization. Essential to the miniaturization of equipment are improvements in optics and exciting developments are expected from optical chip technology in hysteroscopy, such as the Invisio Digital Hysteroscope (GyrusACMI/Olympus, Tokyo, Japan). Portability is also becoming increasingly important such that hysteroscopy can be performed in a variety of community settings. The Endosee® office hysteroscopy system incorporates a disposable inflow cannula light lead and camera and a reusable lightweight handset incorporating a tiny touch LCD screen. Other similar and totally disposable systems are likely to be developed or ones compatible with smart devices to provide imaging and data recoding.

One of the biggest challenges in hysteroscopy is to improve pain relief and acceptability of procedures in the outpatient setting. Not only is research needed to improve the technology, but also research is needed to optimize technique and patient selection. The further refinement of tissue removal systems and evaluations of how they compare with bipolar electrosurgery for polyps and fibroids will be forthcoming. The Symphion™ system (Boston Scientific) is a new, tissue removal system utilizing radio-frequency energy and direct intrauterine fluid pressure monitoring.

For endometrial ablation, future developments will focus on improvements to existing technologies, such as miniaturization, portability, disposability and shortened treatment times, and the development of new technologies with utilizing a variety of previously tried and new energies such as cryotherapy, microwave energy, and steam.

The main disadvantage of hysteroscopic sterilization is that women need to find an alternative form of contraception for at least 3 months while

the fibrosis and occlusion of the tubes occur. Even after 3 months, occlusion will not occur in 1–12% of women (Duffy et al. 2005; Levie and Chudnoff 2006; Sinha et al. 2007). Future developments will focus on techniques that will occlude the tubes in such a way as to provide immediate contraception.

19 Conclusion

Operative hysteroscopy has an increasing role in the management of uterine problems causing abnormal uterine bleeding and reproductive failure and can be used to provide sterilization. Treatments have shown to be safe, effective, and an acceptable replacement to more invasive surgery such as hysterectomy, and this is increasingly the case with the development of new operative hysteroscopic technologies such as tissue removal systems and bipolar electrosurgery. There has been an increasing movement, driven by the miniaturization, feasibility, and portability of new endoscopic technologies as well as patient expectations, toward performing procedures, while patients are awake in an office setting. This helps to reduce cost and complications of general anesthesia. Surgeons undertaking operative hysteroscopic procedures should ensure they have a sufficient caseload to maintain their skills and audit performance and outcome. Best practice guidelines should help inform practice. In addition, valid and structured training and accreditation packages for hysteroscopic training need to be implemented and keep pace with contemporary technologies and the evolving evidence.

20 Cross-Reference

- Basic Management of Infertility
- Diagnosis and Management of the Cancer of the Uterus
- Laparoscopic Hysterectomy
- Laparoscopic Myomectomy- Best Practices
- Management of Abnormal Bleeding in Late Reproductive Years
- Management of Pelvic Pain, Dyspareunia, and Endometriosis
- Management of Recurrent Pregnancy Loss
- Management of Uterine Fibroids
- Pathology of the Uterine Corpus
- Treatment of Gynecological Congenital Anomalies

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Laparoscopic Ovarian Cystectomy

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Contents

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Abstract

Laparoscopy has enabled the laparoscopic gynecologic surgeon to manage many gynecologic surgical challenges in a minimally invasive manner. The laparoscopic approach has become the gold standard in the surgical management of ovarian cysts due to innovative changes in surgical instrumentation and the development of new surgical techniques. Benign ovarian cysts such as persistent and symptomatic functional ovarian cysts, corpus luteum cysts, and cystic ovarian neoplasms such as endometriomas or mature cystic teratomas are now managed as an outpatient procedure decreasing cost and recovery time to the patient. Pelvic ultrasound is the most useful imaging tool in the evaluation of an ovarian cyst. Complex ovarian cysts should be considered for removal in the symptomatic premenopausal woman and in all postmenopausal women. The decision to intervene surgically may be complicated and should be individualized for each patient. Aspiration of ovarian cysts is associated with a high rate of recurrence; therefore, cystectomy is the procedure of choice. Ovarian conservation is preferred in the premenopausal woman if at all feasible, and laparoscopic salpingo-oophorectomy is usually the procedure of choice for the postmenopausal woman.

Laparoscopic entry into the abdomen requires a detailed understanding of the vasculature of the anterior abdominal wall.

Techniques may need to be altered depending on a patient's BMI (body mass index), past history of abdominal surgeries, and history of bowel obstruction or hernias. Laparoscopic removal of the ovarian cyst should facilitate intact removal and avoid intraoperative spillage.

Keywords
Laparoscopic • Ovarian • Cystectomy • Functional cyst • Endometrioma • Dermoid • Complex cyst • Simple cyst • Port placement

1 Introduction

Laparoscopy has become a standard surgical approach for many gynecologic procedures in the last 40 years. It has now become the standard treatment of choice for surgical management of ectopic pregnancies and persistent and/or symptomatic adnexal masses and diagnosis and surgical treatment of endometriosis. The laparoscopic surgical approach has also enabled surgeons to offer minimally invasive hysterectomies.

When laparoscopy was initially utilized in gynecologic surgery, it was limited to diagnostic procedures and tubal ligations. The repertoire of the laparoscopic approach has evolved in the last 20 years as a result of the development of new innovations involving more advanced equipment, improved imaging with new camera systems, and improved expertise in surgical technique. In recent years, newer surgical approaches have developed. In particular, robotic-assisted laparoscopy and, very recently, single-port laparoscopy are gaining more popularity with laparoscopic surgeons. As with the development of any new procedures, the actual roles of these procedures in gynecologic surgery are controversial, and their role remains to be well defined.

Scientific data has consistently supported the laparoscopic approach to the adnexal mass as the preferred treatment. It has been estimated that approximately 10 % of women in the United States will undergo a surgical procedure for an adnexal mass in their lifetime (Hilger et al. 2006). Laparoscopy has also been consistently shown to be associated with decreased postoperative complications such as fever, infection, postoperative pain, and blood loss. Decreased length of hospitalization and overall cost offer additional advantages compared to laparotomy (Yuen et al. 1997; Fanfani et al. 2004; Medeiros et al. 2008).

Despite the abovementioned advantages, laparoscopy should be considered to involve similar surgical risks to laparotomy such as anesthesia risks, infection, injury to intra-abdominal and pelvic organs, and bleeding. Unique risks are also associated with the laparoscopic approach. These risks include the risk of damage to organs and vasculature with laparoscopic port placement and intravascular carbon dioxide gas insufflation with use of pneumoperitoneum to perform surgery. The use of cautery or ultrasonic energy sources also introduces another element of risk to damage to intra-abdominal structures.

1.1 Ovarian Cysts

Ovarian cysts can occur at any stage in life from fetal life through menopause. They can be symptomatic or asymptomatic and found incidentally on clinical exam or on imaging.

The most common types of benign ovarian cysts that the gynecologist encounters include functional cysts (follicular, hemorrhagic, and corpus luteum cysts), mature cystic teratomas (dermoids), endometriomas, and serous and mucinous cystadenomas (Table 1).

1.2 Functional Cysts

Most ovarian cysts develop as a result of faulty ovulation where the follicle fails to release an oocyte. Gradually, a cyst forms because the follicular cells continue to secrete fluid and the fluid accumulates. The cysts are referred to as follicular cysts, and they often resolve spontaneously and do not require surgical intervention (Nelson and Gambone 2010).

Another type of functional cyst is a corpus luteum cyst. The actual mechanism of how the cyst forms is not well understood. This cyst can become quite large and cause symptoms, may be

Table 1 Classification and characteristics of benign ovarian cysts

Functional ovarian cysts	
Follicular cyst	Common in reproductive age women
Corpus luteum cyst	Common in reproductive age women; forms when the corpus luteum fails to regress, may be hemorrhagic
Benign cystic ovarian neoplasms	
Epithelial cell tumors	Derived from mesothelial cells lining the peritoneal cavity and ovary
	Examples: serous cystadenoma, mucinous cystadenoma, endometrioma
Germ cell tumors	Derived from germ cells: may contain ectoderm, mesoderm, or endoderm
	Cystic mature teratoma dermoid cyst
Sex cord-stromal tumors	Derived from sex cords and stroma of developing gonad; may cause feminizing/virilizing effects
	Examples: granulosa-theca cell tumor, Sertoli-Leydig cell tumor

(Beckmann et al. 2006; Nelson and Gambone 2010)

associated with a delay of menses, and is more apt to undergo torsion due to the increased size when compared to the follicular cyst.

1.3 Benign Cystic Ovarian Neoplasms

These cysts are usually categorized due to the cell type of origin such as surface epithelium, germ cell, or sex cord-stromal cells. The majority of these cysts are benign. At least 30 % of ovarian masses in women over the age of 50 are malignant (Kinkel et al. 2005). The risk of malignancy significantly increases in the postmenopausal woman with a cystic neoplasm (Beckmann et al. 2006).

Epithelial cell tumors are thought to develop from mesothelial cells that line the ovary and peritoneal cavity. Cystic epithelial tumors account for approximately 60 % of all true ovarian neoplasms. The endometrioma, serous cystadenoma, and mucinous cystadenoma fall into this category.

Serous and mucinous cystadenomas are typically thin walled, unilocular, or multilocular and can range widely in size. Mucinous cystadenomas tend to be multilocular and much larger than serous cystadenomas. The peak incidence of serous and mucinous cystadenomas is in the fourth to fifth decade. One-third of all ovarian tumors are serous and two-thirds of those are benign. Mucinous epithelial tumors account for 10–15 % of all epithelial neoplasms and 75 % are benign (Goldberg 2015).

Serous tumors are bilateral 25 % of the time, whereas mucinous tumors have a much lower incidence of bilaterality ranging 2–3 % (ACOG 2007). The incidence of bilaterality should be taken into consideration and discussed with the patient at the time of evaluation, particularly if surgical management is required.

The origin of the endometrioma is controversial. Several investigators favor the theory that the endometrioma originates as invaginated endometrial glands on the surface of the ovary (Hughesdon 1957; PPe 1957; Nezhat et al. 1992; Brosens et al. 1994). The endometrioma tends to develop very slowly over time and tends to be moderate in size averaging 5–6 cm in size.

Endometriomas are hormonally active with the menstrual cycle. This often translates into exacerbation of symptoms just prior to and during menses for the patient. The endometrioma can also present a challenge in removal of the capsule to the surgeon. The capsules tend to be very adherent to adjacent ovarian tissue and often are only able to be partially removed which may increase risk of recurrence if ovarian conservation is desired.

Mature cystic teratomas (dermoid cysts) are also common benign cystic ovarian neoplasms. Dermoid cysts account for 10–20 % of ovarian neoplasms and have an incidence of bilaterality of 8–14 %. They are also the most common benign ovarian tumor in the second and third decade of life (Killackey and Neuwirth 1988). They are commonly composed of multiple cell types derived from one or more of the three germ cell

layers (Hamilton 2015). They are almost always benign but can undergo malignant transformation in 0.2–2 % of cases (Comerci et al. 1994; Hamilton 2015)

Historically, laparoscopic management of mature cystic teratomas was not pursued due to concerns regarding the risk of chemical peritonitis in the event of intraoperative spillage of the cyst's sebaceous contents. Recent evidence has not supported this concern. Nezhat et al. noted an incidence of 0.2 % of chemical peritonitis with review of 10 years of experience (Nezhat et al. 1999) It is now very feasible to remove a dermoid cyst via laparoscopic cystectomy.

Simple ovarian cysts up to 10 cm are likely to be benign at all ages with the incidence of malignancy <1 % (Modesitt et al. 2003). There is little evidence in the literature to guide practitioners on which asymptomatic cysts may be ignored or followed. The decision to proceed with surgical interventions usually is usually based upon many factors and individualized for each patient. Cysts that continue to grow or become more symptomatic are more likely to undergo surgical treatment.

2 Workup

The vast majority of pelvic masses are benign in the premenopausal woman. The initial workup should include a medical history, physical exam, serial beta-HCG, CBC, and ultrasound imaging. Depending on the presentation, physicians may also elect to check serial hematocrits and cervical cultures if a hemorrhagic cyst or abscess is suspected. Many cysts can and should be managed expectantly if infection, pregnancy, or torsion have been excluded (ACOG 2007).

Cystic ovarian masses that are symptomatic with pain, pressure, or fever often require immediate intervention such as antibiotics for a tubo-ovarian abscess, medical or surgical management for an ectopic pregnancy, or surgical management for a suspected ovarian torsion.

The postmenopausal woman with a cystic adnexal mass requires a higher index of suspicion for malignancy. The initial workup in addition to a medical history and physical exam should include transvaginal ultrasound imaging and a CA 125 level. Ultrasound findings that raise suspicions for malignancy include solid areas in the mass, excrescences, and free fluid in the abdomen and/or pelvis. The ovary is also a common site of metastases for other primary cancers such as the breast, uterus, colorectal, or gastric cancers. The additional workup of the postmenopausal woman with a suspected malignancy or complex cystic mass should include breast exam, mammogram, digital rectal exam, endometrial biopsy, and upper and lower gastrointestinal endoscopy.

There is no single presurgical evaluation, blood test, and imaging modality that can definitively determine if an adnexal mass is benign or malignant. A definitive diagnosis of the adnexal mass can only be made with surgical excision and histologic evaluation. However, as previously mentioned, the vast majority of cystic adnexal masses are benign (Valentin et al. 2006). In addition, ultrasonographic findings associated with a simple ovarian cyst, endometrioma, or dermoid cysts are quite characteristic and highly predictive of histologic diagnosis.

Many studies support that a thorough preoperative workup will decrease the possibility of performing a laparoscopy in evaluation for a malignant mass (Whiteside and Keup 2009). If a malignancy is suspected, then a laparotomy is the initial proper surgical management. Unfortunately, a CA 125 level, pelvic ultrasound, or peritoneal cytology is not sufficient to rule out a suspected malignancy. Therefore, the decision often rests on the surgeon's intraoperative evaluation and judgment at the time of laparoscopy on whether to proceed with salpingo-oophorectomy and/or laparotomy for suspected malignancy.

2.1 Imaging

Pelvic ultrasound remains the preferred imaging modality to evaluate adnexal cysts.

A simple cyst appears as a round or oval anechoic space with smooth thin walls and no solid component or internal flow on Doppler (Levine et al. 2010). Color or Doppler flow is used to evaluate a complex cyst for internal flow

in solid areas or septations. The principle with Doppler flow is that new vessels within tumors have lower resistance to blood flow because of no smooth muscle in the vessel walls (Helm 2015). At this time, the current role of color Doppler in evaluation of pelvic masses remains controversial because the ranges in the values of the resistive index, pulsatility index, and maximum systolic velocity between benign and malignant masses overlap considerably (ACOG 2007).

Complex cysts typically have ultrasound findings with more than one compartment, referred to as multilocular, thickened walls, papillary projections into the cyst itself or on the surface of the ovary, or abnormal-appearing areas inside the cyst. These findings can be associated with many benign neoplasms or malignant tumors of the ovary. Ultrasound is also helpful in differentiating from other adnexal masses such as hydrosalpinges, paraovarian or tubal cysts, or leiomyomata. Transvaginal, transabdominal, or both need to be utilized to fully evaluate the entire cystic structure. Transabdominal ultrasound imaging is better in evaluating large masses and other findings associated with them such as free fluid or ascites and hydronephrosis.

Other imaging modalities such as the CT, MRI, or PET are not routinely recommended in the initial workup for a cystic mass. The MRI, however, can be very useful in evaluating pelvic masses such as pedunculated leiomyomata or masses that are not adequately evaluated with ultrasound imaging. The CT is most useful in detecting metastatic disease when malignancy is suspected on initial workup.

2.2 Serum Markers

Serum markers are not useful as a routine screening test even though CA 125 levels are elevated in 85 % of patient with epithelial ovarian carcinomas. The value is normal in 50 % of patient with stage 1 cancers confined to the ovary and in 20–35 % of advanced stage ovarian cancer cases (Jacobs and Bast 1989; ACOG 2011). CA 125 levels are also not very specific and are also elevated in patients with some benign conditions such as pregnancy, infection, menstruation, fibroids, endometriosis, cyst rupture, renal failure, and peritoneal inflammation.

Many other potential serum markers are undergoing current research. Their role in the detection of precancer or cancer of the ovary remains yet to be determined.

The presence of at least one of the following indicators warrants consideration of referral to or consultation with a gynecologic oncologist:

Postmenopausal women: elevated CA 125 level, ascites, a nodular or fixed pelvic mass, or evidence of abdominal or distant metastasis

Premenopausal women: very elevated CA 125 level, ascites, or evidence of abdominal or distant metastasis (ACOG 2011)

3 Management

3.1 Observation

Simple functional cysts have been traditionally managed with hormonal suppression with oral contraceptives. However, recent meta-analyses have demonstrated no difference between suppression with oral contraceptives and expectant management in terms of resolution of the ovarian cyst. In premenopausal women, 70 % of adnexal masses will resolve over several menstrual cycles (Curtin 1994). As a result, it is now the standard of care to observe simple ovarian cysts up to 8 cm through several menstrual cycles and follow-up ultrasound imaging for resolution (Grimes et al. 2009). Oral contraceptives are no longer recommended for suppression to facilitate resolution of ovarian cysts (ACOG 2010). Observation is generally not recommended for ovarian cysts $\geq$8 cm due to increased risk of ovarian torsion.

Postmenopausal women with asymptomatic simple ovarian cysts and a normal CA 125 level may also be followed expectantly with serial ultrasound examinations. Some data supports that in this scenario, simple cysts up to 10 cm can also be followed and observed (Bailey et al. 1998). Close follow-up care is very important because the risk of a malignant ovarian neoplasm increases from

13 % in premenopausal to 45 % in postmenopausal patient (McDonald and Modesitt 2006).

3.2 Surgical Intervention

Persistent and/or symptomatic simple ovarian cysts >5–10 cm in size should be considered for surgical removal. Complex ovarian cysts should be considered for surgical removal in the symptomatic premenopausal female. With the exception of simple ovarian cysts on a transvaginal ultrasound finding, most pelvic masses in postmenopausal women will require surgical intervention. The decision to intervene surgically may be complicated and involve many factors and should be individualized based on the clinical scenario and associated findings.

3.3 Laparoscopy

The use of laparoscopy is constantly expanding in gynecologic surgery. It has become the preferred surgical approach for the management of symptomatic or persistent benign ovarian cysts, depending on the experience and skill of the surgeon. This includes suspected endometriomas, hemorrhagic cysts, dermoids, functional cysts, or cystadenomas that have not resolved with expectant management or are symptomatic. Typically, endometriomas, dermoid cysts, or cystadenomas do not resolve spontaneously. Quite often, the diagnosis of a serous or mucinous cystadenoma is not made until laparoscopic evaluation and subsequent removal via cystectomy or oophorectomy.

3.4 Aspiration of Cyst

Aspiration of an ovarian cyst at the time of laparoscopy is generally not recommended unless it is used to facilitate a laparoscopic ovarian cystectomy. Even in the situation of cystectomy, this should only be carried out in an endoscopic bag to avoid spillage in the event of an unsuspected malignancy. If aspiration is solely used to manage an ovarian cyst, there is a high recurrence rate of the cyst approaching up to 65 % (Mesogitis et al. 2005). In addition, there is no tissue for pathologic evaluation and malignancy cannot be ruled out. It has also not been proven more effective than expectant management (Zanetta et al. 1996).

Aspiration of ovarian cysts is contraindicated in postmenopausal women due to concerns regarding the increased potential for malignancy. Evidence shows that there is demonstrated decrease survival of stage 1 ovarian cancer patients if spillage occurs intraoperatively compared to patients with tumors removed intact (Cuesta et al. 1994; Mizuno et al. 2003).

3.5 Laparoscopic Ovarian Cystectomy

The optimal surgical goal is to remove the entire cyst intact. The cyst should be removed inside a laparoscopic bag so that inadvertent spillage into the peritoneal cavity may be avoided. If an oophorectomy is performed, the ovary with the intact cyst should be removed contained within an endoscopic bag.

Very large benign-appearing ovarian cysts are now being managed more commonly via the laparoscopic approach. In this approach, the ovary is usually placed in an endoscopic bag and drained of excess fluid and then removed within the bag through a small incision (Eltabbakh et al. 2008). This approach obviously avoids a large laparotomy incision and facilitates a faster recovery with decreased morbidity and cost for the patient.

Ovarian conservation is generally the goal in a premenopausal woman with a benign ovarian cyst requiring surgical excision. The advantage is preservation of viable ovarian tissue and thus fertility and hormone production. Oophorectomy and possibly bilateral salpingo-oophorectomy may be elected in surgical management of a postmenopausal woman with a benign cyst. Oophorectomy may also be considered for premenopausal women who are considered for increased genetic risk for ovarian cancer.

Entry into the abdomen may be performed with several techniques. In a Cochrane review of 46 randomized controlled trials comparing various techniques, there was no advantage of using any single technique in preventing vascular or visceral complications. There is insufficient evidence to recommend on laparoscopic entry technique over another (Ahmad et al. 2008).

An understanding of the anterior abdominal wall vessels is of paramount importance to avoid injury to these vessels. There are two sets of bilateral vessels, the superficial and inferior epigastric vessels. The vessels are located an average of 5.5 cm from the midline. The lateral ports should be placed approximately 8 cm from the midline to avoid vascular injury. Transillumination of the anterior abdominal wall with the laparoscope to visualize the superficial vessels is recommended during placement of lateral ports. It is also optimal to try and visualize the inferior vessels intra-abdominally with visualization of the laparoscope whenever possible.

In patients with a history of prior abdominal surgery, there is a risk of 20 % of adhesions to the anterior abdominal wall involving the omentum or bowel (Vilos et al. 2007). As a result, surgeons may elect to gain entry with any of the three following techniques: the closed entry with the Veress needle, open laparoscopy, or left upper quadrant placement at Palmer's site.

3.6 Standard Closed Entry

The Veress needle may be used to create a pneumoperitoneum prior to laparoscopic port placement. The needle is advanced into the peritoneal cavity usually through a 5 mm incision at the umbilicus. During placement of the Veress needle, the abdominal wall is elevated by using two perforating towel clamps placed just lateral to the umbilicus and lifting up during insertion or manually grasping and lifting the abdominal wall superior to the suprapubic area during insertion. The abdominal wall is elevated to maximize the distance between the abdominal wall and retroperitoneal vessels. Entry into the peritoneal cavity may be confirmed with the saline drop test and observation for pressure less than 8 mmHg during insufflation. The CO2 gas is then insufflated into the needle to create a pneumoperitoneum. Maximum insufflation pressure is usually set at 15 mm but can be increased to 20 mm if needed and tolerated by the patient. Once this pressure is obtained, then an adequate pneumoperitoneum is obtained, and the surgeon can now proceed with umbilical primary port placement.

Hurd et al. (1991) characterized the difference in abdominal wall thickness and how it can influence laparoscopic port entry. In women with ideal body weight (body mass index, [BMI] <25 kg/m^2), the Veress needle is inserted toward the hollow of the sacrum at a 45° Fig. 1a). The retroperitoneal vessels are much closer to the abdominal wall, and there may be as little as 4 cm between the skin and these vessels in thin patients. In the obese patient (BMI >30 kg/m^2), a more vertical approach, approximately 70–80°, is necessary to enter the peritoneal cavity because of increased thickness of the abdominal wall (Fig. 1c).

Open laparoscopy may also be performed to gain entry into the abdominal cavity. There is no evidence to support that overall open entry is superior or safer than the other entry techniques (Ahmad et al. 2015).

Surgeons may elect to gain entry via the left upper quadrant in the event that periumbilical adhesions are suspected, patient has a history of umbilical hernia, or there are failed attempts at entry via the umbilicus. With this technique, the Veress needle is advanced through a 5 mm incision at Palmer's point, which is at the midclavicular line just beneath the lower rib margin and pneumoperitoneum created with insufflation of CO2 gas. A 5 mm laparoscopic port is then advanced into the peritoneal cavity and confirmed with visualization with the laparoscope.

Direct laparoscopic port placement is considered safe without a pneumoperitoneum when done with disposable blunt trocars. It is also faster than the Veress needle technique and is not associated with insufflation-related injuries because proper placement is confirmed with visualization with the laparoscope prior to insufflation. This is performed while elevating the abdominal wall with perforating towel clamps or manually

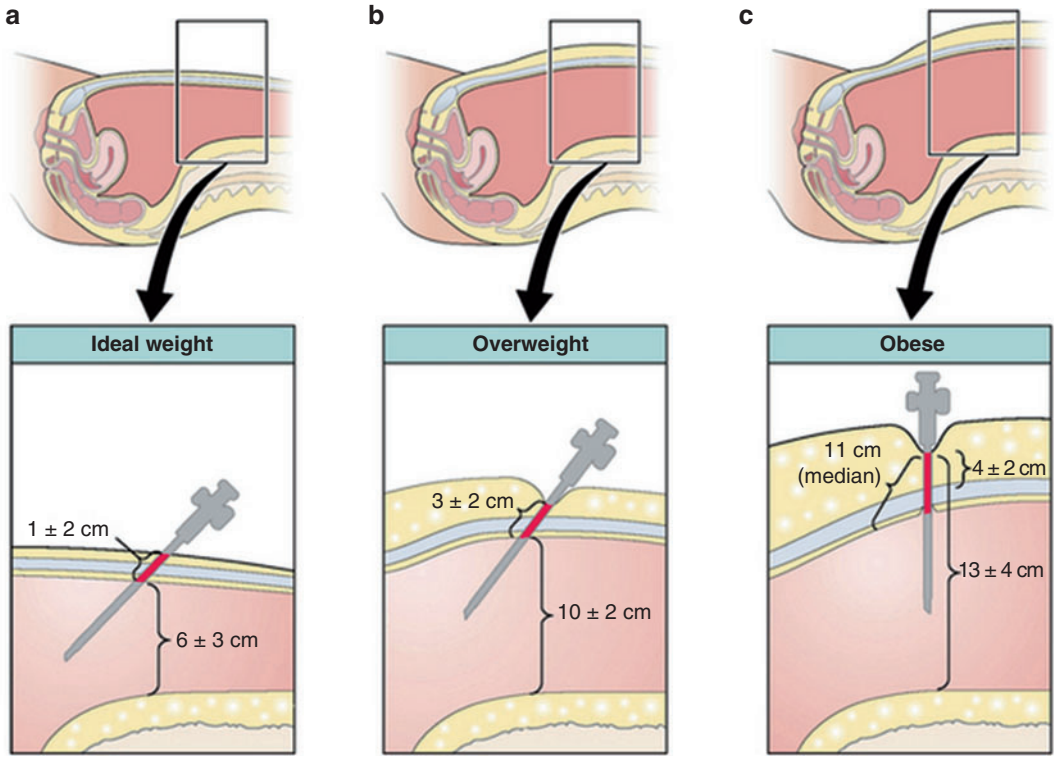

Fig. 1 Differences in umbilical trocar placement in patients with different BMIs (body mass index) (Adapted from Hurd et al. 1991)

grasping the abdominal wall and elevating it. Elevation of the abdominal wall during trocar insertion maximizes the distance between the umbilicus and the retroperitoneal vessels. Elevation of the abdominal wall during trocar or Veress needle placement, however, does not necessarily guarantee visceral or blood vessel injury.

The initial laparoscopic port is usually placed at the umbilicus with a 5–12 mm port. The pelvis is carefully surveyed, and the ovarian cyst is examined for any signs that may be suggestive of malignancy such as ascites, excrescences on the surface of the ovary, and implants noted on peritoneal, liver, or diaphragm surfaces. Five millimeter ports are then placed laterally. The surgeon may opt to obtain cell washings at this time for cytology. If the cyst appears benign, then cystectomy is performed.

Cystectomy is then performed by incising the capsule of the ovary with endoshears or the surgeon's preferred laparoscopic power source. The cyst is then enucleated carefully with traction and countertraction and dissection as needed. If intraoperative rupture occurs, particularly with a dermoid cyst, the peritoneal cavity should liberally be rinsed with normal saline or Ringer's lactate that has been shown to be safe (Nezhat et al. 1999; Zanetta et al. 1999; Milingos et al. 2004).

After the cyst is removed from the ovary, an endoscopic bag is then advanced through the umbilical 10–12 mm port, and the cyst is placed in the bag. If a 5 mm umbilical port was used for initial survey, this port can be exchanged for a 10–12 mm port. The bag is then advanced up to the umbilical incision, and the port is removed while advancing the edges of the bag through the skin incision. The bag is then opened and triangulated to facilitate removal of the cyst intact if small enough or with morcellation carefully avoiding any spillage out of the bag. Prior to removal, the cyst may need to be drained while in the bag. Once the specimen is small enough, the

bag is removed with the specimen through the incision. Other options for removing the specimen include a minilaparotomy or colpotomy. If colpotomy is performed, antibiotics are recommended.

If concern about the benign nature of the cyst exists, the cyst wall should be sent for frozen section at the time of removal. If malignancy is confirmed or suspected, then the procedure should be converted to a laparotomy for continued appropriate surgical management.

After removal of the bag and specimen, the 10–12 mm laparoscopic port is replaced through the umbilical incision and the camera advanced through the port. The ovary is then carefully inspected for hemostasis. Bleeding from the bed of the cyst in the ovary may require measures to obtain hemostasis. Hemostasis in the bed of the ovary at the site of the cystectomy has traditionally been accomplished with bipolar cautery. This may also be performed with use of other laparoscopic power sources or application of a hemostatic agent. Recent evidence suggests that the application of hemostatic sealants such as FloSeal (Baxter International Inc., Deerfield, IL) or Surgicel fibrillar (Ethicon, Inc., Somerville, NJ) results in improved ovarian reserve after cystectomy compared to cautery (Song et al. 2014). The edges of the ovarian capsule do not need to be reapproximated as is traditionally done with an open ovarian cystectomy. Some surgeons prefer to utilize an adhesion barrier product on the ovary to minimize postoperative adhesion formation.

The procedure is completed by irrigation of the pelvis, and a careful survey of the pelvis for hemostasis with the intraperitoneal pressure decreased to 5 mmHg. The port sites are then inspected for hemostasis. After all port sites are inspected for hemostasis, the C02 peritoneum is then allowed to escape through the umbilical port. Care is taken to ensure that as much gas is expressed as possible to minimize postoperative discomfort for the patient and to avoid the bowel being pushed into the incision sites as residual gas escapes. The incisions are then closed with suture, Steri-Strips, or a skin adhesive. Fascial closure is recommended for ports 10 mm or greater in size prior to skin closure to prevent subsequent development of an incisional hernia (Tonouchi et al. 2004).

Simple cysts in postmenopausal women can also be removed laparoscopically since the vast majority is benign. However, salpingo-oophorectomy is generally considered the procedure of choice.

3.7 Contraindications to Laparoscopic Ovarian Cystectomy

Absolute contraindications to ovarian cystectomy continue to be controversial. The presence of a known malignancy has traditionally been considered an absolute contraindication. As expertise increases with laparoscopy, there is currently disagreement regarding this concept. The use of laparoscopy in the setting of surgical management of malignancy continues to develop and expand. Laparoscopic staging and management of ovarian cancer have been reported (Fauvet et al. 2005; Lecuru et al. 2006). However, there are reports in the literature that suggest that laparoscopy may increase the risk of port-site metastases and intraperitoneal spread of cancer cells (Morice et al. 2004; Nagersheth et al. 2004; Ramirez et al. 2004). Continued experience will further define the role of laparoscopy in the surgical management of ovarian malignancy.

Relative contraindications have also changed over the past 30 years since laparoscopy has improved with advances in surgical technique and equipment. Previously, obese patients or patients with a history of multiple abdominal surgeries or bowel obstructions were considered not to be candidates for the laparoscopic approach. Open laparoscopy, left upper quadrant access, and the use of trocars with optical access capabilities are now widely accepted techniques for such patients.

Table 2 Summary of indications for oophorectomy

Benign ovarian neoplasms not amenable to treatment with cystectomy, enucleation, partial oophorectomy
Elective or risk-reducing salpingo-oophorectomy
Adnexal torsion with necrosis
Ovarian malignancy
Tubo-ovarian abscess unresponsive to antibiotics
Definitive treatment for endometriosis
Gastrointestinal or other metastatic cancers
Male pseudohermaphrodites

Valea and Mann (2015)

3.8 Oophorectomy

Indications for oophorectomy as the preferred procedure are noted in the Table 2 below (Valea and Mann 2015).

Oophorectomy and most commonly laparotomy are the procedures of choice rather than cystectomy in women with an ovarian mass that is suspicious for malignancy. Oophorectomy is the preferred management for any ovarian mass that requires surgical intervention in postmenopausal women regardless of the suspicion for malignancy.

Laparoscopic oophorectomy is usually performed as a salpingo-oophorectomy. The infundibulopelvic ligament and the ureter are carefully identified. The ureter is easily identified through the peritoneum in most patients. If the ureter is difficult to identify, the peritoneum must be opened and dissection carried out retroperitoneally to facilitate location of the ureter. The procedure is then carried out with ligation of the infundibular pelvic ligament, the utero-ovarian ligaments, and the fallopian tube next to the cornua of the uterus. This can be performed with a variety of techniques including bipolar electrocautery, ultrasonic cutting and coagulation devices (e.g., Harmonic scalpel), bipolar vessel-sealing devices (e.g., LigaSure, EnSeal, Gyrus-PK), loop technique, or stapling devices. The ovary and fallopian tube are then placed in an endobag and brought up to the umbilical port-site incision and removed in a similar technique to the cystectomy. Cyst fluid may be carefully aspirated from the cyst while enclosed in the bag to facilitate removal through the port-site incision with care taken to avoid any spillage into the peritoneal cavity. If malignancy is suspected, morcellation of the ovary is not recommended to preserve optimal pathologic evaluation. If the ovary cannot be removed via the bag through the laparoscopic port, then a larger incision is required for safe removal.

4 Conclusion

Laparoscopic ovarian cystectomy has now evolved to become the gold standard of surgical management of benign cystic ovarian masses in premenopausal women. The development of improved laparoscopic camera systems and instruments has enabled surgeons to evolve and continually improve their laparoscopic surgical techniques. In addition, the role of minimally invasive approaches continues to gain increased acceptance with gynecologic oncologists in the management of possible malignancies.

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Robotic Surgery in Gynecology: Indications, Advantages, Avoiding Complications

John P. Lenihan Jr

Abstract

The use of computers to assist surgeons in the operating room has been an inevitable evolution in the modern practice of surgery. Robotic assisted surgery has been evolving now for over two decades and has finally matured into a technology that has caused a monumental shift in the way gynecologic surgeries are performed. Prior to robotics, the only minimally invasive options for most gynecologic procedures including hysterectomies were either vaginal or laparoscopic approaches. However, even with over 100 years of vaginal surgery experience and more than 20 years of laparoscopic advancements, most gynecologic surgeries in the United States were still performed through an open incision. That changed in 2005 with the introduction of the da Vinci Surgical Robot™ for gynecology. Over the last decade, the trend across the country has now dramatically shifted to less open and more minimally invasive procedures. Robotic assisted procedures now include not only hysterectomy but also most all other commonly performed gynecologic procedures including myomectomies, pelvic support procedures, and reproductive surgeries. This success however has not been without controversies particularly around costs and complications. The evolution of computers to assist surgeons and make minimally invasive procedures more common is clearly a trend that is sustainable. It is now incumbent on surgeons, hospitals, and medical societies to determine the most cost-efficient and productive use for this technology.

Keywords

Robotic assisted surgery • Hysterectomy • Myomectomy • Credentialing and privileging

Contents

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1 Introduction

Robotic surgery is actually surgery performed by a skilled surgeon with the assistance of a computer utilizing a remote **telesurgery** platform (Herron and Michael Marohn 2007). Remote surgery has been a dream for the last century. In the late 1980s, DARPA (Defense Advanced Research Projects Agency) funded a remote surgery program targeted for the battlefield. Researchers at Stanford University (Stanford Research Institute or SRI), developed early technology around telepresence. Many civilian companies and labs worked on robotics such as IBM who developed remote center technology, MIT who developed cable-driven technology for low friction manipulators, and Computer Motion who developed the first surgical robot, ZEUS. In 1990, researchers at SRI formed a company that licensed these technologies and started the long process of turning a good idea into a product. They merged with their primary competitor at the time, Computer Motion and formed Intuitive Surgical (Sunnyvale, CA), the developer of the **da Vinci Surgical Robotic System™**. This system was the only commercially available robot from the late 1990s to 2015. Today, other manufacturers are entering the marketplace with new novel robotic systems.

2 Early Days

Initially, the surgical robot was designed for battlefield use with predominantly vascular capabilities. However, urologists soon found the robot was a great surgical approach to prostate cancer surgery, and the commercial version took off. Lonnie Smith, the first CEO of Intuitive Surgical, said that, initially, the company "aimed for the heart but hit the prostate instead." In June 2005, the FDA approved the da Vinci Robot™ for use by gynecologists. Because hysterectomies are the second most common surgery done in the United States, it didn't take long for GYN to surge to the top of the robotic surgery adoption curve. The initial robot, the "standard system, evolved" to an "S" model with improved high-definition 3-D vision and easier docking technology. In 2010, the "Si" next-generation model was introduced. It had a more flexible bedside cart (the actual robot) as well as improved technology that allowed the development and use of newer instruments such as vessel sealers, staplers, as well as new imaging modalities such as infrared and fluorescence. It also was the platform for the first robotic single-site technology that allowed surgeons to perform single-site surgery with the help of the computer to make it less challenging for surgeons who were used to operating in a 2-D laparoscopic world. The latest robot model was introduced in 2014: the "Xi." This robotic platform is designed for complex multi-quadrant abdominal surgery such as cancer surgery (Figs. 1, 2, 3 and 4). Future platforms for Single Port™ surgery from Intuitive Surgical and from competitors such as TransEnterix (Alf-X™) and Titan Medical (Sport™) will bring welcome competition to this market and lead to more innovation that will ultimately benefit surgeons and patients (Figs. 5 and 6).

3 Single Site

Reduced port laparoscopic surgery has been a goal of most minimally invasive surgeons since the dawn of laparoscopy. The drawbacks of fewer ports decreased the ability of the surgeon to utilize instruments in a typical comfortable fashion to dissect tissue and particularly to sew. Single-site techniques such as single-incision laparoscopic surgery (SILS), laparo-endoscopic single-site (LESS), and single-site surgery (SSS) have been reported since the 1990s, but these have been slow to catch on with most gynecologic surgeons

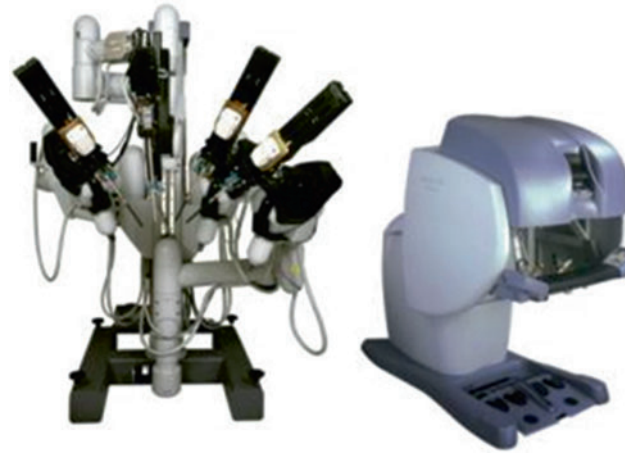

Fig. 1 Original DaVinci™ Standard Robotic Surgical System

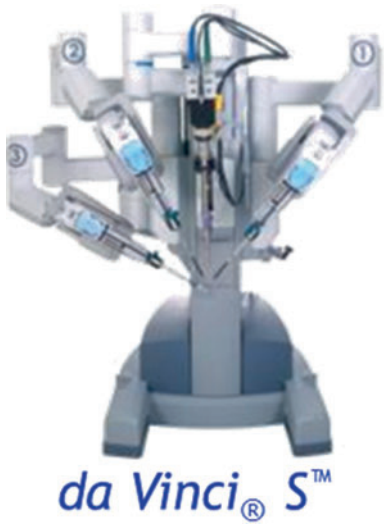

Fig. 2 DaVinci™ S

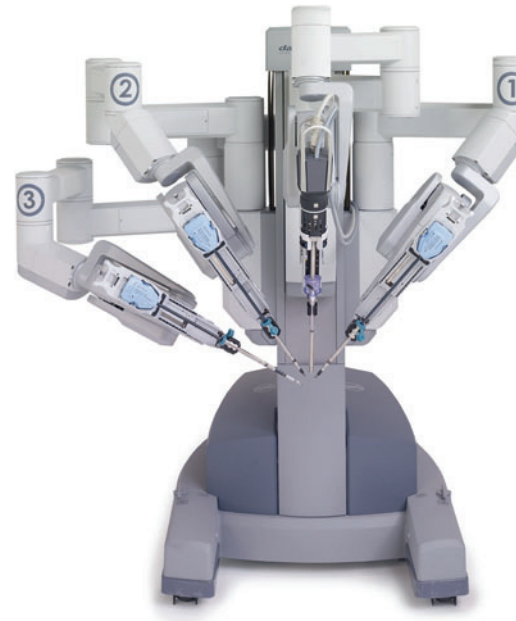

Fig. 3 DaVinci™ Si

primarily due to the long learning curves and the requirement for exceptional innate ability to perform laparoscopy. In 2014, Intuitive Surgical released a modification of their Si robot that allowed surgery to be performed robotically through a single site. This four channel port housed the camera, an accessory channel, and two non-wristed robotic instruments. The robotic microprocessors converted the surgeon's hand control to operate the left arm instrument with the surgeon's right hand, which was now on the patient's right side, and vice versa. This allowed the surgery to proceed like normal robotic surgery and not require "cross vision" which was typical of straight stick single-site laparoscopy. Recently in 2015, a wristed needle driver was added to this platform making suturing more like traditional robotics. Future developments are aiming to increase the mobility and articulation of the instruments as well as the camera flexibility to provide a more ergonomic and standardized procedure.

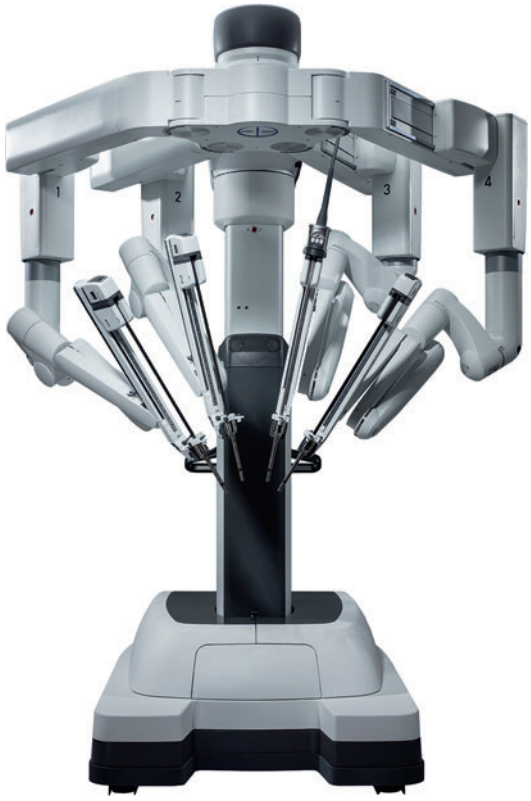

Fig. 4 DaVinci™ Xi

4 Robotic Advantages

The computer-assisted enhancement of robotics has many advantages over straight stick laparoscopy. The most significant advantage acknowledged by most all surgeons is the advantage to see the operative field in **high-definition 3-D** with a stable camera platform controlled by the surgeon. Additional advantages include wristed instruments with **articulation** that goes beyond the normal ability to manipulate instruments, scaled motion to allow for more precise movements, and a significant **ergonomic** benefit of being able to sit comfortably in a console rather than standing upright at the bedside trying to watch a remote video monitor while moving rigid instruments into small spaces. Disadvantages of robotic surgery pointed out by many include the loss of **haptic feedback** (touch), which many surgeons feel is integral to being a good surgeon. Another drawback is limited ability to communicate with the OR team while the surgeon is task focused in the robotic console. Team training with "**cockpit communication**" techniques employed by the aviation industry helps to minimize this limitation. That being said, many surgeons who did not feel comfortable performing hysterectomies or other complex gynecologic procedures with traditional laparoscopy have

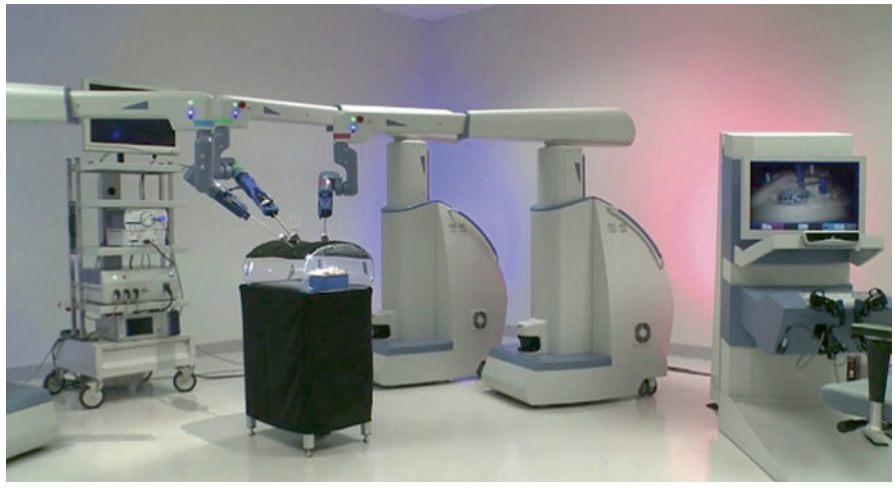

Fig. 5 TransEnterix Alf-X Robotic platform

Fig. 6 Titan Medical Sport™ Robotic System

found the robot to be an enabling device allowing them to convert open procedures to minimally invasive operations.

As robotic technology evolves, there are now enhancements to the robot that provide even more advantages to the surgeon. The Si and Xi robots have the capability of visualizing **infrared** without additional equipment. This enables surgeons to see infrared ureteral catheters (Stryker InfraVision™), which may help to identify ureters in the face of complex pathology and thereby prevent an inadvertent ureteral injury. **Fluorescence imaging** utilizing dyes that fluoresce with laser stimulation such as indocyanine-green dye (ICG Dye) have proven useful in identifying sentinel lymph nodes, aberrant blood vessels, and even endometriosis implants, again enabling surgeons to see structures that might otherwise not be visible with the naked eye. Future developments being studied now include improved single-port capabilities, "GPS" guidance for surgeons using overlayed imaging technology such as ultrasound and MRI, and even remote co-surgery using internet-connected consoles to allow expert surgeons in academic centers to operate with primary surgeons in their local facilities.

5 Gynecology Adoption

Initially, the robot seemed most useful for enabling surgeons to perform complex minimally invasive procedures more easily for the surgeon than most surgeons could perform with laparoscopy. Laparoscopy is a minimally invasive technique that has been utilized by gynecologists since the mid-1970s. In the 1980s, surgeons started attempting more complex procedures requiring dissection and sewing, and in 1989, Dr. Harry Reich reported the first total laparoscopic hysterectomy (Reich 1989). In 2003, Dr. Arnold Advincula reported an initial series of robotic myomectomies which at the time were typically accomplished by almost all gynecologists as an open procedure (Advincula et al. 2004). Subsequently, after the da Vinci Robot™ was approved for gynecology surgeons, many reports were published evaluating it as a new tool compared to laparoscopy (Advincula and Song 2007). **Learning curves** were defined as being more extensive than was initially suspected, and early adoption associated with complications was reported in national media, prompting the legal profession to become interested in robotic surgery and advertise for patients injured by the robot (Carreyrou 2010). It became clear that while robots were enabling, they didn't substitute for good surgical technique and judgment. Based on this, professional societies sought to provide guidance for the proper utilization of this expensive technology as well as recommendations for training and credentialing (ACOG technology assessment in obstetrics and gynecology No. 6: robot-assisted surgery 2009; AAGL Guidelines: Guidelines for Privileging for Robotic-Assisted Gynecologic Laparoscopy 2014).

The rapid adoption of computer-assisted telesurgery by gynecologists had led to a dramatic change in the route of hysterectomy in the United States. Traditionally, rates of abdominal

hysterectomy surgery have been very high approaching 60–70% (CDC-MMWR 2002; Jacobsen et al. 2006). The minimally invasive approaches to hysterectomy seemed to be stuck at 25% for several decades for the vaginal approach and less than 15% for the laparoscopic approach (CDC-MMWR 2002; Jacobsen et al. 2006). With the adoption of robotic hysterectomy in 2005, the rate of TAH has dropped across the country to <40% (Wright et al. 2013a).

There have been many controversies regarding robotic surgery, however, mostly based on the high cost of the surgical robots. Many medical societies are now pushing to limit the robot to skilled surgeons performing complex surgeries and to encourage most gynecologists in the communities to use less expensive minimally invasive approaches such as vaginal or laparoscopic hysterectomy (Rardin 2014; Advincula 2014).

6 Hysterectomy

Hysterectomy is one of the most common surgical procedures performed in the United States. While the numbers of hysterectomies have fallen over the last decade due to a variety of other less-invasive options for managing abnormal uterine bleeding, hysterectomy is still considered the definitive treatment for many gynecologic conditions and has a high satisfaction rate among patients when compared to other simpler but often less-effective treatments (Pinion et al. 1994; Dickersin et al. 2007). Initial reports by experienced laparoscopic surgeons who started to perform robotic assisted surgeries showed that similar outcomes could be achieved compared to laparoscopic procedures but that operative times were often much longer. The **learning curve** to become proficient for experienced expert gynecologic surgeons has been shown to be between 50 and 100 cases (Lenihan et al. 2008; Seamon et al. 2008; Payne and Dauterive 2008). Gynecologic oncologists have reported extensive data showing the advantages of robotic surgery for complex cancer surgeries (Bell et al. 2008; Estape et al. 2009; Sert and Abeler 2011). Initially, these surgeries were limited to **endometrial cancers** with pelvic lymph node staging, but now there are many series showing excellent results compared to laparoscopic and traditional open surgeries for cancers requiring para-aortic node dissection, radical hysterectomies for **cervical cancer,** and even **ovarian cancer** staging procedures (Magrina et al. 2011).

The role of robotic surgery in benign hysterectomy has been more debated based primarily around **cost issues**. Many studies have shown increased costs associated with robotic surgery over other forms of hysterectomy. One well-publicized study used a large national payor inpatient database and showed that for low-volume surgeons (average <12 procedures per year), quality outcomes with robotics were not different than with laparoscopic surgery but that the cost for robotic cost surgery was higher. This study was done, however, when almost all of the robotic surgeons were still in the early stages of their learning curves. Also, capital costs of the robot were factored in but not laparoscopic equipment capital costs. And finally, this study evaluated surgeons who only performed on average ten cases per year (Wright et al. 2013b).

More recent publications comparing costs among experienced high-volume robotic surgeons have shown that these differences return to negligible once surgeons are through their learning curves (Lim et al. 2016).

Additional studies have looked at outcomes for robotic hysterectomies in patients with very large uteri who would typically not be candidates for laparoscopic or vaginal surgery and would in most instances require a traditional open procedure. These studies showed again excellent outcomes with a minimally invasive approach in the hands of experienced surgeons (Payne et al. 2010).

7 Myomectomy

The da Vinci Robot has wristed instruments with five degrees of motion similar to a surgeon's natural wrist motion. This allows surgeons to overcome one of the most difficult tasks associated with traditional "straight stick" laparoscopy: sewing. Removing fibroids is a sewing intensive

surgical procedure, hence, one for which the robot is ideally suited. Minimally invasive myomectomy was an uncommon procedure prior to the development of the da Vinci Robot. Despite three randomized trials showing the superiority of laparoscopic myomectomy over open myomectomy, less than 3% of gynecologic surgeons performed laparoscopic myomectomies on at least 50% of their patients (Gargiulo 2011). Being able to use multiple instrument arms and wristed instruments of the robot enabled surgeons to perform myomectomies with multiple layer myometrial closures comparable to what could be achieved in an open procedure. Multicenter trials have reported excellent outcomes both for the procedure itself as well as for **subsequent pregnancies**. In a large series by Pitter et al., 107 women out of 872 myomectomies over a 5 year period conceived 127 pregnancies and 92 deliveries. Uterine rupture occurrence was minimal (one patient), and adhesions were found in 11% at the time of cesarean section (Pitter et al. 2013). Most robotic myomectomy procedures experienced minimal blood loss with a same-day discharge and rapid return to normal activities (Advincula et al. 2011; Ascher-Walsh and Capes 2010; Barakat et al. 2011).

8 Sacrocolpopexy and Pelvic Suport Procedures

A sacrocolpopexy is another sewing intensive surgery that requires precise dissection techniques as well as excellent sewing skills. Laparoscopic sacrocolpopexy (SCP) was shown in the late 1990s to have excellent outcomes comparable to open procedures (Ross and Preston 2005). But like myomectomy, this procedure required an advanced skill set for any surgeon who wanted to perform this surgery with traditional straight stick laparoscopy. The da Vinci Robot™ was utilized by early pioneers to perform mesh sacrocolpopexies with or without hysterectomy. These initial procedures had long operative times, especially while the surgeons were early in their learning curves; however outcomes were comparable (Geller et al. 2008). One randomized controlled sacrocolpopexy trial was done that also showed longer operative times but similar length of stay and outcomes (Paraiso et al. 2011). This study however compared expert laparoscopic surgeons with surgeons who had done less than ten robotic surgeries, so the learning curve effect was not taken into account. Subsequent publications have shown improved operative times and improved outcomes with experienced surgeons who do a high volume of these procedures (Ploumidis et al. 2014). Recent controversies surrounding the use of synthetic mesh in pelvic organ prolapse repairs have shown a lower incidence of mesh erosion with sacrocolpopexy than with vaginally placed mesh used for anterior and posterior repairs. Almost all of the Female Pelvic Medicine and Reconstructive Surgery (FPMRS) fellowships across the country now teach robotic approaches to sacrocolpopexy to their fellows (Occhino et al. 2013).

8.1 Endometriosis and Chronic Pelvic Pain

Patients who suffer from endometriosis can have more complex pathology and adhesions than patients with cancer. Traditionally, most surgeons performing diagnostic laparoscopy for **chronic pelvic pain** patients have limited options for dealing with extensive endometriosis and inflammatory adhesions based on the limitations of traditional laparoscopy and the surgeon's innate abilities. Most experts now recommend aggressive surgical excision of endometriosis implants and adhesions in patients with advanced and chronic disease (Hart et al. 2005; Shakiba et al. 2008). Meta-analyses have shown no benefit to surgery in patients with early-stage disease when comparing surgery to medical therapy for the treatment of pain, although there has been some benefit if **infertility** is considered (Giudice 2010; John and Hummelshoi 2013). Another potential advantage of robotics over traditional laparoscopy for treating endometriosis is associated with the enhanced high-definition 3-D vision afforded by the robotic system which may give surgeons an increased ability to recognize endometriotic lesions with this enhanced visual capability. The

use of laser-enhanced dyes that identify vascular lesions has also been studied recently to increase the ability of surgeons to recognize endometriosis (Lue et al. 2015). This technology, called Firefly by Intuitive Surgical, is not yet approved by the FDA for this purpose and is still under IRB approved investigations. There have also been reports of surgeries to transect pelvic nerves, such a presacral neurectomies, to help with chronic central pelvic pain and dysmenorrhea in younger patients wishing to preserve fertility (Kapetanakis et al. 2012). The dissection of the presacral space is challenging with regard to identifying the major vessels as well as the nerves in this area. The enhanced visual capabilities of the da Vinci Robot along with the wristed and scaled motion of the instruments allow for this dissection to be done by surgeons who are not comfortable working in this space with traditional laparoscopic instruments.

8.2 Reproductive Surgery

The da Vinci Robot™ has been used by reproductive surgical specialists to try and restore normal anatomy in patients requesting future childbearing. The ability to lyse **adhesions** carefully and gently, similar to laparoscopy, has shown better outcomes when compared to open surgery. Some authors have reported series of tubal reanastamosis after prior tubal ligation to restore fertility with good outcomes (Falcone et al. 1999; Dharia Patel et al. 2008). While this technique facilitates excellent repairs with good results based on the enhanced 3-D high-definition vision and micro dexterity associated with the robot, these procedures have not been widely adopted due primarily to costs as well as the availability of other successful fertility techniques such as in vitro fertilization (IVF).

8.3 Ovarian Cysts

Use of the robot has also proven helpful in the management of complex and large ovarian cysts such as **dermoid cysts** (benign cystic teratomas) as well as other benign and even malignant neoplasms (Magrina et al. 2009). The robot enables many surgeons to enucleate the cysts and preserve the ovary compared to those surgeons simply removing the ovary with laparoscopy. The use in functional and hemorrhagic cysts has not been widely adopted based primarily on the fact that most surgeons can manage those problems more easily conservatively without surgery or with traditional laparoscopic approaches. Also, since many of these procedures are emergencies, many surgeons do not have the availability of a robot late in the day after normal OR hours.

9 Special Populations

Obesity is becoming epidemic in the United States with dramatic increases in obese and very obese populations across the country over the last decade. Surgery in obese patients has been demonstrated through the years to have higher risks and complications related to wound healing, ventilation, and anesthesia problems and management of common comorbid medical conditions in the intra- and postoperative phases (Early 1995). An ideal surgery for a morbidly obese patient would allow the surgeon to operate in a precise fashion with comfortable ergonomics and would also reduce wound complications and other risks associated with bariatric patients. This definition fits robotics.

Many studies have shown the clear benefits of robotic surgery in this population (Scheib et al. 2011; Gehrig et al. 2008). Many of these studies have involved malignant hysterectomies, which require more extensive surgery including lymph node dissection, particularly challenging in the laparoscopic environment. With the adoption of robotic surgery, many programs have seen a significant increase in the numbers of obese patient who are now able to have a minimally invasive procedure; and in addition, most authors report significantly reduced or even no **conversions to open** which were common in at least half of patients prior to robotics (Veljovich et al. 2008).

9.1 Complications

As with many new technologies, it didn't take long for the robot to attract the attention of malpractice attorneys. While initially promoted as enabling technology by Intuitive Surgical, the manufacturer of the da Vinci Robot ™, it soon became clear that new surgeons were attempting much more difficult and challenging surgeries than they ever would have tried with traditional laparoscopy. It is also clear that many new surgeons did not fully accept the learning curve of 50–100 cases, which led them to tackle more complex cases than they were prepared for in their early adoption of robotic surgery. This has led to the recognition of an increase in robotic surgery injuries occurring in the early years after initial approval by the FDA in 2005 (AndoniN et al. 2008; Manoucheri et al. 2014).

In retrospective studies, the reported incidence of complications for robotic surgery is 2–10%, and the complications identified include bowel, vascular, bladder, ureteral, and nerve injuries. Incidence of complications for robotic surgery is lower than for open surgery; but outcomes were no different in a retrospective comparison of perioperative outcome for robotic versus laparoscopic hysterectomy (Patzkowsky et al. 2013).

9.2 Direct and Indirect Injuries

Complications of robotic surgery can occur as a result of malfunction of the robotic system, surgeon inexperience and poor technique, improper patient positioning, and other unrelated factors such as trocar injuries. The incidence of robotic system failure during surgical procedures has been reported to be 2.4% for robotic general surgical procedures and 4.5% for robotic urologic and gynecologic procedures (Patzkowsky et al. 2013; Kim et al. 2009; Agcaoglu et al. 2012; Finan and Rocconi 2010). Reported injuries can be broken down into robot-caused (direct) and robot-associated (indirect) injuries. Direct injuries are injuries to other structures such a bowel laceration caused by the surgeon tearing the bowel serosa with one of the robotic arms or energy related injuries such as a thermal burn to the bowel or a vessel caused by electricity sparking from the robotic instrument to that structure. Delayed thermal injuries from the heat generated by cautery can result in late tissue necrosis of the ureter, bowel serosa, or other vulnerable structures.

Indirect injuries are injuries related to the use of the robot such as vaginal hysterectomy **cuff dehiscence**. Cuff separation and cuff dehiscence are well-known complications of any hysterectomy. Newer studies have reported an increased incidence of dehiscence after both laparoscopic and robotic surgeries (Koo et al. 2013; Uccella et al. 2012). No specific cause has been identified, but many experts feel it is a combination of tissue desiccation from the use of cautery on the tissue and closing the cuff with suture bites that are too small but seem large to the surgeon based on the magnified vision provided by the robot. No specific suture or method of closure has been identified as being more at risk for this problem. Many prudent surgeons are now, however, using delayed absorbable sutures as well as restricting their patients from vaginal activity or sexual relations for 6–8 weeks after surgery. Barbed delayed absorbable horizontal running sutures are commonly used for cuff closure.

9.3 Preventing Complications

Often, many factors contribute to surgical complications. This is particularly true for surgeons who utilize robotics. Working in the surgeon console remote from the patient's bedside, surgeons must have excellent **communication** with the other members of the operating room team. A good example of this is in preventing a lost suture needle. An excellent technique for preventing missed communication has been developed by the aviation industry called "cockpit communication." This technique requires the copilot or other crew member to state the communication back to the pilot. For example: "Landing gear down?" "Landing gear down." An operating room example would be: "Needle out?" "Needle out." Having the first assist or surgical techs reply back to

the surgeon after every query using this technique is an excellent safety measure.

Another issue is **task saturation** by the surgeon. Often, a surgeon can get so focused on the dissection and process of the surgery that they lose track of the time in the operating room. Having a patient immobilized in unusual positions such as Trendelenburg position for prolonged periods of time can lead to numerous problems such as neuropathy, facial edema, and respiratory difficulties (Scheib et al. 2011). Many institutions have adopted second "**time-outs**" after a designated period of time such as 4 h and then every 2 h after that (Song et al. 2013). This helps get the entire team communicating as to the status of the patient and helps the surgeon and the team decide if they can safely continue or should consider converting to a different approach.

The most common cause of direct robotic complications, however, is that the surgeon is not prepared for the pathology that they find at the time of surgery. Poor exposure, inadequate instrumentation, and failure to plan for unusual emergencies all play a role in most complications. **Surgical planning** and preparation is the single most important step a surgeon can take to minimize complications (Gawande 2011). There are many courses available every year through university medical schools, societies such as the American Association of Gynecologic Laparoscopists (AAGL)-Advancing Minimally Invasive Gynecology Worldwide, and even industry sponsored advanced and master's sourses which focus on new techniques, complex anatomy, and proper patient selection for the robotic approach.

10 Training, Credentialing, and Privileging

Initial training pathways were developed by Intuitive Surgical that focused on how to operate the robot. Typically, these training classes involved a computer-based learning module, hands-on practice with operating and docking the robot, and a pig or cadaver lab or equivalent. Proctored cases were required although the numbers varied and there was no standard pathway or recommendation. Subsequently, learning curve studies were published showing that in the hands of accomplished laparoscopic surgeons, learning curves for robotic surgery were much longer than was originally thought (Lenihan et al. 2008; Seamon et al. 2008; Payne and Dauterive 2008). Recent studies have demonstrated that for gynecologic oncologists and urogynecologists, the learning curve to become proficient was over 91 cases (Woelk et al. 2013).

Recently, the national news media such as the Wall Street Journal has reported on robotic surgery complications that have now brought the whole issue of training and credentialing into focus (Carreyrou 2010). Hospitals are also being sued for failing to provide adequate oversight. In July 2015, the State of Washington Supreme Court upheld a lower court decision in *Taylor v. Intuitive Surgical* that hospitals had the primary responsibility to oversee training and privileging of surgeons, not surgical device manufacturers such as Intuitive Surgical (Estate of Fred Taylor v. Intuitive Surgical Inc. n.d.; Ostrom 2013).

Many highly reliable industries such as aviation and nuclear energy have systems in place to train and verify competency on an ongoing basis. Most hospitals do not have such systems. Surgeons are automatically recredentialed every year based on lack of serious adverse events. The aviation industry uses a model based on standardized initial training, progressing from simple activities to more complex activities as one becomes more experienced, continued certification based on numbers of procedures done such as takeoffs and landings (currency), and annual or biannual proficiency testing done with either check rides with a check-pilot examiner or passing simulation exercises or both. This aviation based model was adopted by the in March 2014 as a recommendation for Initial and Ongoing Privileging and Certification for Robotic Surgery (AAGL Guidelines: Guidelines for Privileging for Robotic-Assisted Gynecologic Laparoscopy 2014; Lenihan 2011, 2014). It focuses on standardized training pathways, requiring surgeons to only do basic cases initially, utilize simulation on a regular basis, and set a minimal number of cases per year to maintain privileges at 20. Many

hospitals have chosen to use lower annual surgical currency numbers due to pressure from low-volume surgeons who still wish to offer robotics to their patients. Others have pointed out that currency numbers insure higher volume but do not always correlate with skill or patient outcomes despite many articles correlating better outcomes with higher volume surgeons (Wallenstein et al. 2012). Recently, innovative robotic surgeons have utilized **crowdsourcing** to evaluate technical skills and surgical judgment by reviewing robotic surgical videos, (www.csats.com) (Lendvay and Kowalski 2015). This innovative approach is more objective and has the potential to replace currency numbers with actual graded assessments of technical skill and judgment insuring that hospitals meet the legal and Joint Commission requirements of oversight of their surgeons.

Robotic surgery training at the residency and fellow level presents additional challenges. Obstetrics and gynecology residents are required by American Board of Obstetrics and Gynecology (ABOG) to have performed at least 70 hysterectomies prior to completing their training programs in order to qualify for board certification. Hysterectomy rates have declined dramatically in the United States over the last decade due to a number of causes, and many programs are not able to meet this number. In addition, residency directors are challenged with which approaches to teach their residents. Shorter residency work week and hour restrictions limit time available for training. This contributes to resident perception of not feeling competent to perform minimally invasive procedures after graduation without additional training (Burkett et al. 2011).

The **residency training network** (RTN) was developed in 2012 by a group of robotic surgeons who were residency program coordinators. This group developed standardized teaching models for training future robotic surgeons. It relies heavily on simulation to teach psychomotor skills and requires its students to become proficient by passing these exercises prior to considering them adequately trained to perform robotic surgery. Cognitive training is also being developed to teach anatomy and surgical steps in procedures such as hysterectomy. Currently, there are over 70 residency training programs that are members of this network. More information can be found at www.robotictraining.org.

11 Summary and Conclusions

Robotic assisted gynecologic surgery is a significant technological advancement that utilizes computers to help surgeons become more successful at offering their patients a minimally invasive approach to almost all gynecologic conditions. There have been controversies regarding this approach, primarily focused on increased costs without significant benefits when compared to laparoscopic or vaginal surgeries in the hands of expert surgeons. These are real issues especially in our current health-care system, and the costs of robotic surgery need to be addressed by hospitals and medical societies. It is up to individual hospital systems to determine the most cost-effective ways to use robotic surgery and to encourage surgeons to use less costly methods when possible on patients who qualify for those approaches (Rardin 2014; Advincula 2014). Current cost studies however have looked at direct costs and have not accounted for the most part in cost savings due to reductions in open surgeries as well as decreased conversions and short term readmissions. A retrospective study by Martino et al. measured procedure-related **readmissions** within 30 days of discharge after benign hysterectomy in 2554 patients in an academic hospital system. Patient's undergoing robotic assisted laparoscopic hysterectomy (RALH) had a significantly lower chance of readmission <30 days after surgery when compared to laparoscopic, abdominal (open), and vaginal approaches. They also experienced shorter length of stay (LOS), lower estimated blood loss (EBL), and significant cost savings associated with readmission when compared to non-robotic approaches (Martino et al. 2014). Under the Affordable Care Act (ACA), environment, hospitals, and surgeons are paid for better outcomes and penalized for complications. This type of information should clearly be factored into future

analyses of the relative value of robotic surgery (Liberman et al. 2012).

Complications initially were thought to be higher with robotic surgeries, but with increasing experience, these seem to be equivalent to other techniques and have been associated more commonly with low-volume surgeons as well as with surgeons who are in the early stage of their learning curves. Robotic surgery is still in its relative infancy compared to other surgical approaches. As technology advances, computer-assisted robotic surgery will continue to advance and provide enabling benefits to both surgeons and to their patients in the future. There is a significant need to create prospective studies and registries in order to further assess best practices, costs, and outcomes so that future surgeons will be better prepared with good data to make appropriate choices for how to deliver surgical care to their patients.

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Minimally Invasive Procedures for Incontinence and Lower Urinary Tract Disorders: Indications and Avoiding Complications

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Abstract

Stress urinary incontinence is a common condition affecting women. When conservative therapy is unsuccessful in relieving symptoms, several minimally invasive options exist for the surgical management of stress incontinence. Women with stress incontinence symptoms, post-void residual less than 150 ml, negative urinalysis, a positive cough stress test, no pelvic organ prolapse beyond the hymen, and urethral hypermobility are candidates for an anti-incontinence procedure without preoperative urodynamic testing. The retropubic and transobturator mid-urethral sling procedures have an efficacy of approximately 85% and low rate of complications. The transobturator approach avoids passage into the retropubic space and minimizes the risk of bladder, bowel, and major vessel injury but is associated with higher rate of neurologic symptoms. Postoperative voiding dysfunction after the mid-urethral sling is low and can be managed with sling loosening in the first few weeks after surgery or simple sling transection later in the postoperative period. The mid-urethral slings have been shown to have similar efficacy to the Burch colposuspension. The retropubic mid-urethral sling appears to be more successful in women with Valsalva leak point pressure $\leq$60 cm H_2O and maximum urethral closure pressure $\leq$20 cm H_2O. The laparoscopic Burch colposuspension offers an alternative to the mid-urethral sling for women who are already having a laparoscopic procedure or who wish to avoid the use of permanent mesh. A maximum urethral closure pressure $\leq$20 cm H_2O is generally considered contraindication to a Burch colposuspension procedure. Outcomes appear to be similar to the open Burch colposuspension and mid-urethral sling.

Keywords

Mid-urethral sling • Transobturator sling • Retropubic sling • Laparoscopic colposuspension • Laparoscopic Burch

1 Introduction

Urinary incontinence is a common condition among women. Estimates of prevalence vary depending on the definition used, the question asked, and the patient population, but in a racially diverse sample of noninstitutionalized women over the age of 20 in the United States, almost 50% of women reported symptoms of urinary incontinence (Dooley et al. 2008).

Over 250,000 anti-incontinence operations are performed in the United States each year (Haya et al. 2015). Minimally invasive therapies for stress urinary incontinence fall into two categories: the mid-urethral sling and the laparoscopic colposuspension. Ulmsten and colleagues first described the minimally invasive mid-urethral sling in 1996 (Ulmsten et al. 1996). The transobturator sling was introduced in 2001 (Delorme 2001). The retropubic and transobturator mid-urethral sling procedures have now become the most commonly performed procedure for stress urinary incontinence; approximately two-thirds of anti-incontinence procedures in the United States are mid-urethral slings, and the rate is as high as 98% in Sweden (Haya et al. 2015). Laparoscopic retropubic colposuspension was first described in the early 1990s (Taylor and Tsokos 1993), but the procedure has been less widely adopted by surgeons, most likely because it is more technically challenging than the mid-urethral sling procedure. However, it offers a minimally invasive option for women who prefer to avoid the use of a permanent implant.

2 Indications for Surgery

Surgery for stress incontinence is indicated in women bothered by these symptoms, who request treatment, and when more conservative therapies have been unsuccessful. Stress incontinence is defined as the complaint of involuntary loss of urine on effort or physical exertion (such as sporting activities) or on sneezing or coughing (Haylen et al. 2010). Conservative therapies shown to be effective include pelvic floor exercises, with or

without biofeedback or pelvic floor physical therapy, timed voiding, fluid management, and weight loss in overweight and obese patients. Even moderate weight loss can be effective. In a randomized trial comparing a 6-month weight-loss program with a structured education program in overweight and obese women with urinary incontinence, women in the 6-month weight-loss program had a mean weight loss of 8.0% (7.8 kg) and a reduction in weekly incontinence (mostly stress urinary incontinence) of 47% compared to 1.6% (1.5 kg) and 28% in the structured education program, respectively ($p < 0.001$) (Subak et al. 2009).

Urodynamic stress incontinence is the involuntary leakage of urine during filling cystometry, associated with increased intra-abdominal pressure, in the absence of a detrusor contraction. However, urodynamic testing is not mandatory before planning on surgery for stress incontinence. In women with uncomplicated stress incontinence, urodynamic testing has not been shown to improve the outcome of surgical intervention (Nager et al. 2012). Uncomplicated stress urinary incontinence is defined as post-void residual urine volume less than 150 mL, negative urinalysis, a positive cough stress test result, and no pelvic organ prolapse beyond the hymen. It is important to demonstrate objective evidence of stress incontinence. This can be done with a cough stress test in which the patient is asked to cough with a full bladder, initially in lithotomy position and then in standing position if no leak is demonstrated in lithotomy. It may be necessary to retrograde fill the bladder if the patient does not have a full bladder. If leak cannot be demonstrated with a cough stress test or if the patient has an elevated post-void residual volume, urodynamics is indicated.

Lack of urethral hypermobility is a relative contraindication to most anti-incontinence procedures as a higher rate of failure has been demonstrated (Richter et al. 2011). Urethral hypermobility is generally defined as a resting angle or displacement angle of the urethra–bladder neck with maximum Valsalva of at least 30° from the horizontal (Zyczynski et al. 2007).

The Burch colposuspension has been shown to have a higher failure rate in women with maximum urethral closure pressure $\leq$20 cm H_2O (Sand et al. 1987), and this would generally be considered a contraindication to the procedure, whether performed via an open abdominal incision or laparoscopically. Low leak point pressure $\leq$60 cm H_2O, however, does not appear to be a risk factor for failure of the Burch colposuspension (Hsieh et al. 2001).

3 Mid-urethral Sling

The mid-urethral sling was originally described in 1996 by Ulmsten and colleagues. The tension-free tape (TVT; Gynecare, Ethicon Women's Health and Urology, Somerville, New Jersey, USA) was first introduced in the United States in 1998. The TVT introduced several modifications to the traditional bladder neck slings resulting in a revolutionary change to the management of stress urinary incontinence. These modifications were (1) mid-urethral placement (rather than at the bladder neck), (2) no suture fixation of the sling mesh, (3) no tension placed on the urethra, and (4) minimal dissection. The transobturator sling offered a lower risk of certain complications by avoiding significant retropubic passage of the needle.

4 Retropubic Mid-urethral Sling

4.1 Technique

The retropubic mid-urethral sling (Fig. 1) is most commonly performed as a bottom-up procedure as originally described by Ulmsten and colleagues (1996). There are slight variations in technique depending on the sling kit utilized, and it is important to be familiar with the product available. All of the currently available sling kits use a loosely woven, monofilament polypropylene sling mesh with pore size greater than 75 μm. This type of mesh allows for tissue ingrowth and fibrosis, allowing the mesh to be incorporated into the surrounding tissues as well as allowing for

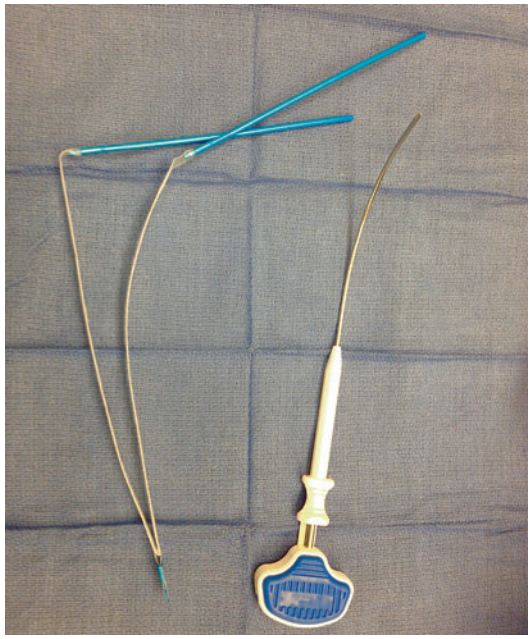

Fig. 1 Photo of a retropubic mid-urethral sling (Advantage Fit sling, Boston Scientific, Natick, MA, USA). The polypropylene sling is covered by a plastic sheath. The sling is attached to the needle for passage. The plastic sheaths allow for easy movement of the sling through the tissue and prevent contamination of the sling before insertion; they are removed once the sling is adjusted below the urethra

migration of macrophages and other leukocytes for infection surveillance.

For the retropubic mid-urethral sling, the patient is placed in low to moderate dorsal lithotomy with an 18 or 20 French Foley catheter to drain the bladder. Two 0.5 cm skin incisions are made just above the pubic bone, i.e., suprapubic, about 2 cm from the midline (Fig. 2a). The skin may be infiltrated with local anesthetic prior to making these incisions. Retropubic hydrodissection is then performed. Saline or local anesthetic may be used (Fig. 3). This is done by starting at the previously made skin incisions and passing an 18 gauge spinal needle along the back of the pubic symphysis until the needle touches the endopelvic fascia. Location of the needle tip is confirmed with a hand in the vagina palpating lateral to the urethra. 20–50 cc of saline (or local anesthesia) is injected on each side. Saline or local anesthetic is also injected along the anterior vaginal wall below the urethra. A sagittal incision no more than 1.5 cm long starting at 1 cm proximal to the urethral meatus is made with a #15 scalpel blade. Lateral periurethral tracks are made with the Metzenbaum scissors. Care should be taken to keep the dissection to full thickness of the vaginal wall. The vaginal dissection should be carried out until the tip of the Metzenbaum scissors touches the interior portion of the inferior pubic ramus. The bladder is emptied, and the rigid catheter guide is inserted into the channel of the Foley catheter (Fig. 4). The tip of the catheter is then pushed toward the posterior lateral wall of the bladder opposite to the intended trocar passage. When passing the right side, the tip of the catheter should be directed toward the left side and vice versa. On the right side, the left hand should hold the trocar handle, and the right hand should be used to control initial insertion of the device. The position of the hands is reversed for the other side. The needle tip is then placed into the vaginal incision. The right index finger is placed under the anterior vaginal wall, just lateral of the suburethral incision. The needle tip is directed horizontally until the urogenital diaphragm is perforated; sometimes a "pop" is felt. This initial push should occur with the palm of the vaginal hand, the hand on the handle being there to ensure stability. At this point, the needle is directed more upward, staying immediately behind the pubic bone, and the trocar handle is dropped. The needle should be aimed toward the previously made skin incisions, and care should be taken not to rotate the handle. There will be resistance once the rectus fascia is reached. At this point, the vaginal hand is removed, and taking care not to rotate the needle, the needle is pushed up through the fascia, muscle, and skin with the hand on the handle. The plastic tip is grasped and the metal guide/needle is removed. The procedure is repeated on the left side. The bladder and urethra are diverted to the patient's right. The right hand now is used to hold the handle, and the left hand is placed vaginally.

Cystourethroscopy with a 70° rigid cystoscope should then be performed to ensure bladder integrity. There are different ways to adjust the mesh, including using an intraoperative cough test as

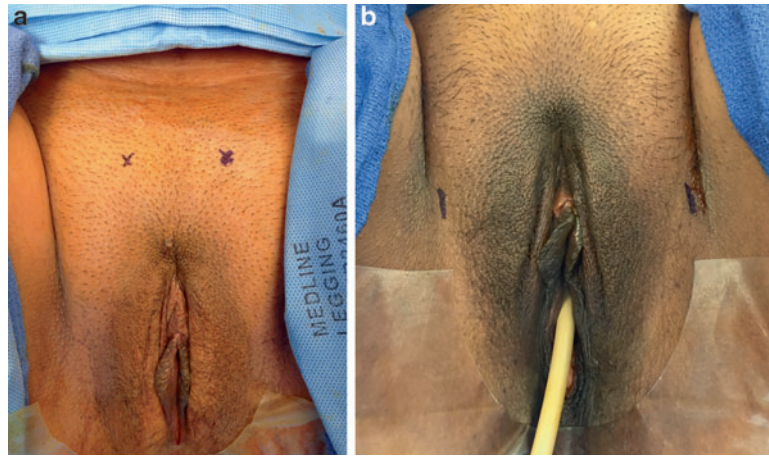

Fig. 2 Markings demonstrate location of suprapubic incisions (**a**) and groin incisions (**b**) for the retropubic and transobturator slings, respectively

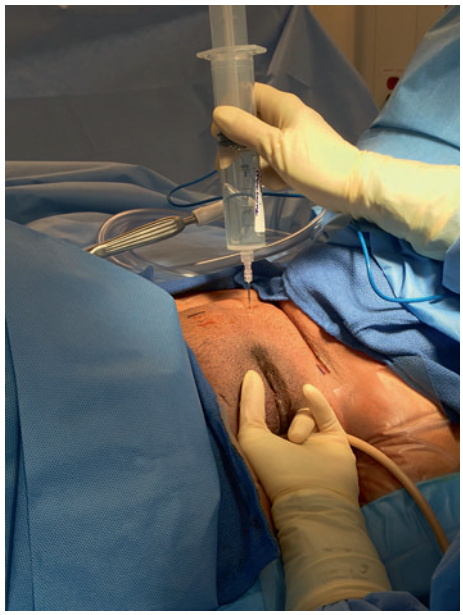

Fig. 3 Retropubic hydrodissection with saline or local anesthetic. An 18 gauge spinal needle is passed along the back of the pubic symphysis until the needle touches the endopelvic fascia. Location of the needle tip is confirmed with a hand in the vagina palpating lateral to the urethra. 20–50 cc of saline (or local anesthesia) is injected on each side

discussed below, but it is important that the mesh is adjusted loosely below the urethra and does not place tension on the urethra. It is often helpful again to have an 18 or 20 French Foley catheter in place when adjusting the sling. A small

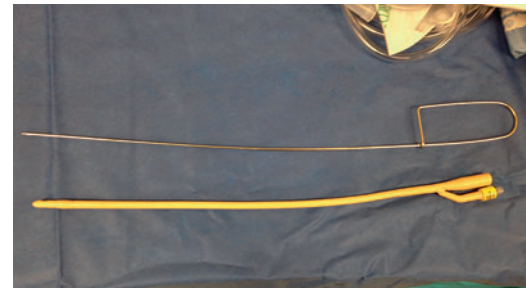

Fig. 4 Rigid catheter guide and Foley catheter

instrument, such as a Kelly clamp, should then be placed between the mesh and the urethra to ensure that the sling does not tighten further during removal of the plastic sheaths (Fig. 5).

Once the plastic sheaths are removed, the vaginal wall incision should be closed with 2-0 or 3-0 delayed absorbable suture, and the skin incisions may be closed with 4-0 monofilament absorbable suture or Dermabond (Ethicon Endosurgery, Inc., Cincinnati, OH). A postoperative voiding trial is mandatory.

The SPARC (Astora Women's Health, LLC, Eden Prairie, MN, USA) differs from the other retropubic slings in that the SPARC needles are inserted through two 0.5 cm incisions just above the symphysis pubis (top-down route). The exit point for the SPARC needles is through the midline vaginal incision. A finger in the vaginal incision guides the exit of the needle.

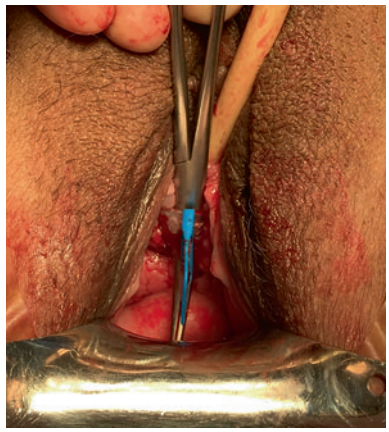

Fig. 5 Adjusting the sling. A small instrument, such as a Kelly clamp, should then be placed between the mesh and the urethra to ensure that the sling does not tighten further during removal of the plastic sheaths

5 Anesthesia and the Cough Stress Test for the Retropubic Mid-urethral Sling

In the initial description of the TVT, Ulmsten described performing the procedure under conscious sedation and local anesthesia and with the use of an intraoperative cough test to adjust the sling. However, this posed a challenge with some patients who either did not do well with this type of anesthesia or had relative contraindications. Surgeons initially began looking into the use of regional anesthesia as an alternative to conscious sedation and local anesthesia. This allowed the intraoperative cough test to be performed and arguably allowed the patient better anesthesia. Wang and Chen randomized 73 women having the TVT procedure to conscious sedation and local anesthesia versus epidural anesthesia (Wang and Chen 2001). Intraoperative cough test was performed in both groups. At a minimum of 12 months of follow-up, there was no difference in subjective or objective outcome. Adamiak and colleagues randomized 103 women having the TVT to conscious sedation and local anesthesia versus spinal anesthesia. Intraoperative cough test was again performed in both groups. They found no difference in subjective outcome 6 months postoperatively (Adamiak et al. 2002). Similarly Liapis and colleagues randomized 86 women having a TVT to conscious sedation and local anesthesia versus epidural anesthesia and found no difference in objective outcome at 12 months (Liapis et al. 2007). However, regional anesthesia has been suggested as a risk factor for early voiding dysfunction. Women who had regional anesthesia had an increased odds (adjusted odds ratio, 4.4; 95% confidence interval, 1.9–10.2) of acute postoperative urinary retention compared with women receiving conscious sedation with local anesthesia or general anesthesia (Wohlrab et al. 2009), and there is concern that the pelvic floor muscle paralysis as a result of regional anesthesia may lead to overtightening of the sling, especially when intraoperative cough test is used to adjust the sling.

Moore and colleagues specifically addressed the question of the cough test intraoperatively in a randomized study of 92 women having the TVT procedure using conscious sedation and local anesthesia for both groups (Moore et al. 2012). Their primary outcome was the proportion of women had a successful voiding trial within 24 h of catheter removal/clamping, and they found no significant difference between both groups. As a secondary outcome, they looked at 24 h pad test and validated quality-of-life questionnaires 12 months postoperatively and found no significant difference between the two groups.

Over time many surgeons began performing the procedure under general anesthesia. While there are no randomized trials, multiple retrospective studies have found no difference in efficacy or complications with general anesthesia versus conscious sedation and local anesthesia or regional anesthesia (Centinel et al. 2004; Ghezzi et al. 2005; Lo et al. 2003; Low et al. 2004; Murphy et al. 2003). Murphy and colleagues prospectively examined a cohort of 170 women having the TVT procedure; anesthesia type was selected at the discretion of the operating surgeon (Murphy et al. 2003). At a median follow-up of 32 months, with 132 (84.6%) of women responding, they found a significantly greater improvement in stress incontinence symptoms as reported by a validated questionnaire in women who had conscious sedation and local anesthesia versus

general anesthesia. However, the data was confounded by the fact that only two surgeons performed all of the procedures, with one surgeon performing almost all the cases under general anesthesia.

The use of local anesthesia as an adjunct to general anesthesia for postoperative pain was examined in a randomized trial of 42 women having a SPARC sling under general anesthesia (Dunivan et al. 2011). The primary outcome, 2 h postoperative visual analogue scale score, was significantly lower in the group that received intraoperative injection of 0.125% bupivacaine along the retropubic path of the sling when compared to the control group (1.9 vs. 2.6 out of 10.0, respectively; $p = 0.05$). There was no difference in the outcome of the voiding trial; in the bupivacaine group, 15/19 (79%) subjects versus 12/19 (63%) in the control group failed the voiding trial (RR 1.25, 95% CI 0.83–1.89). Success rates were not examined in this study.

6 Retropubic Mid-urethral Sling Compared to Open Burch Colposuspension

Ward and Hilton performed the landmark trial comparing the TVT sling with the retropubic colposuspension proving comparable efficacy for the retropubic mid-urethral sling and the retropubic colposuspension (Ward and Hilton 2002). In this multicenter trial, 344 women with urodynamic stress incontinence were randomized to the TVT sling versus the retropubic colposuspension. The primary outcome measure was objective cure of stress incontinence based on a negative 1 h pad test (<1 g change in weight) and a negative stress test on urodynamic testing. At 6 months of follow-up, a negative 1 h pad test was recorded in 128 (73%) patients in the TVT group and 109 (64%) in the colposuspension group. There was no evidence of urodynamic stress incontinence in 142 (81%) patients after the TVT procedure and 114 (67%) after the colposuspension. Objective cure, as defined above, was found in 115 (66%) patients in the TVT group and 97 (57%) in the colposuspension group ($p = 0.099$, Cochran-Mantel-Haenszel test; 95% confidence interval for difference in cure −4.7 to 21.3%). Of the 98 women who had TVT and 79 who had the colposuspension who returned for 5-year follow-up (Ward and Hilton 2008), a negative 1 h pad test was recorded in 58 (81%) women in the vaginal tape group and in 44 (90%) women in the colposuspension group at 5 years. A last observed result carried forward analysis was carried out, in which pad test data from the last available follow-up visit were imputed to substitute missing data. On this basis, the cure rates at 5 years were 75% for TVT and 69% for colposuspension (OR 1.32 [95% CI 0.82–2.12]).

7 Bottom-Up Versus Top-Down Retropubic Sling

When examining the more commonly performed retropubic bottom-up route to the top-down route, subjective cure is higher with the bottom-up route (RR 1.10, 95% CI 1.01 to 1.19; three trials, 477 women) (Ford et al. 2015).

8 Complications of Retropubic Mid-urethral Sling

Certain complications are inherent to the retropubic mid-urethral sling because of blind passage of the needle. Trocar cystotomy occurs in about 5% of cases; with previous pelvic surgery, especially prior to retropubic colposuspension, the risk increases to as high as 31% (Haab et al. 2001). Obesity appears to be protective (Lovatsis et al. 2003). Intraoperative cystotomy does not appear to affect the outcome of surgery and can be managed with short-term (1–3 days) catheterization (La Sala et al. 2006). However, perforation of both the small bowel and the large bowel has been reported as has injury to the external iliac vessels (Aslam and Denman 2013; Castillo et al. 2004; Fourie and Cohen 2003; Leboeuf et al. 2004; Meschia et al. 2002; Sivanesan et al. 2007; Zilbert and Farrell 2001). Careful technique is essential to minimize the risk

of these types of complications. The potential for these types of catastrophic and life-threatening complications made it attractive to find an alternate route of sling placement.

9 Transobturator Sling

9.1 Technique

The outside-in transobturator sling is the most common approach to the procedure. The bladder is emptied before beginning. A large caliber Foley catheter can be helpful to have in place to help identify the urethra during the procedure. The dissection is started with an anterior vaginal wall incision at the mid-urethra (Fig. 6). The vaginal wall can be infiltrated with saline if desired for hydrodissection. Similar to the retropubic mid-urethral sling, the incision usually begins about 1 cm proximal to the urethral meatus and is made to have a length of 1.5–2 cm. The vaginal wall is then incised, and the lateral periurethral tracks are made with the Metzenbaum scissors. It is important that the vaginal dissection be carried out until the tip of the Metzenbaum scissors touches the interior portion of the inferior pubic ramus. To make the skin incisions, first palpate the edge of the ischiopubic ramus; identify the adductor longus tendon insertion to the pubic ramus; then move down along the edge of the ischiopubic ramus to approximately the level of the clitoris. Mark this site just lateral to the bony edge bilaterally and then make stab incisions with a #15 scalpel blade.

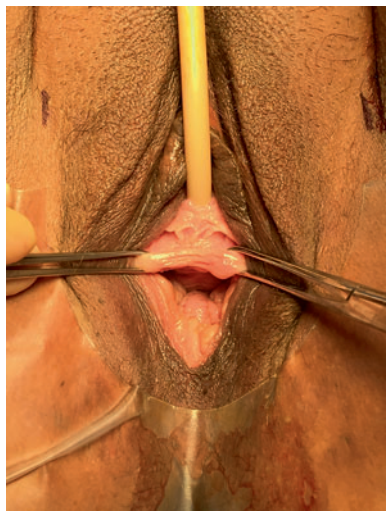

Fig. 6 Location of anterior vaginal wall incision. Allis clamps are used to hold the vaginal epithelium so that an incision can be made at the level of the mid-urethra, starting 1 cm proximal to the urethral meatus

The helical needle is grasped with the contralateral hand. A catheter guide can be placed through the Foley catheter to divert the bladder and urethra to the contralateral side. When passing the helical needle on the left side, the needle should be initially be placed in the previously made skin incisions, perpendicular to the skin, and the index finger of the left hand should be placed in the vaginal incision until the bone is palpable. The thumb from the left hand should be on the outside curve of needle to control the needle movement as it perforates the obturator membrane and muscle. The needle is then pushed in through the obturator membrane and muscle until a "pop" is felt, i.e., until resistance against needle stops. The needle shaft and handle are then positioned at a 45° angle to the patient's vertical axis and close to body and rotated along the posterior surface of the ischial pubic ramus and toward the left index finger that is in the vaginal incision. The index finger will meet the needle tip as it moves around the pubic ramus. If the needle tip cannot be located, then the needle should not be advanced and its position reassessed. It may need to be withdrawn to just behind the pubic ramus and advanced again. It is important at this point to check for perforation at the lateral vaginal sulcus before attaching the mesh. The mesh is then attached to the needle tip and pulled through. The procedure is repeated on the other side.

Cystourethroscopy with a 70° rigid cystoscope is performed at this point to ensure bladder integrity. There are different ways to adjust the mesh, including using an intraoperative cough test, but it is important that the mesh is adjusted loosely below the urethra and does not place tension on the urethra. It is often helpful again to have an 18 or 20 French Foley catheter in place when adjusting the sling. A small instrument, such as a Kelly clamp, should then be placed between the

mesh and the urethra to ensure that the sling does not tighten further during removal of the plastic sheaths.

Once the plastic sheaths are removed, the vaginal wall incision should be closed with 2-0 or 3-0 delayed absorbable suture, such as Vicryl, and the skin incisions can be closed with Dermabond. A postoperative voiding trial is mandatory.

The inside-out technique is used by the TVT-Obturator (Gynecare, Ethicon, Johnson & Johnson, Somerville, NJ, USA). The dissection is the same as above. The safety-winged guide that comes with the kit is inserted into the dissected track and just through the obturator membrane. The helical passer is inserted inward along the winged guide until a "pop" is felt through the obturator membrane with the helical passer. At this point, it is important to immediately stop insertion of the helical passer once tactile feel confirms the membrane has been penetrated. Remove the guide. Reposition the handle of the helical passer by dropping it toward the midline until the handle is nearly vertical to the floor. Rotate the helical passer and hug the ischiopubic ramus, until the skin is tented. Make skin incision at the point where the tip of the helical passer tents the skin. Grasp the exposed tip with a clamp. Stabilize the tube near the urethra and remove the helical passer with a reverse rotation of the handle. Pull the plastic tube completely through the skin until the mesh appears. Repeat the procedure on the other side, perform cystoscopy, and adjust the sling as indicated above.

10 Retropubic Versus Transobturator Sling

The trial of mid-urethral slings (TOMUS) was a multicenter, randomized equivalence trial comparing outcomes with retropubic and transobturator mid-urethral slings in women with stress incontinence (Richter et al. 2010). The primary outcome was treatment success at 12 months according to both objective criteria (a negative stress test, a negative pad test, and no retreatment) and subjective criteria (self-reported absence of symptoms, no leakage episodes recorded, and no retreatment). The investigators found no significant difference in objective (82.4 vs. 79.6% for retropubic vs. transobturator sling) or subjective (62.4 vs. 56.0% for retropubic vs. transobturator sling) cure rate between the two groups. The median estimated blood loss and operative time were both significantly higher in the retropubic sling than in the transobturator sling group (estimate blood loss, 50 ml vs. 25 ml, $p < 0.001$; operative time, 30 min vs. 25 min, $p < 0.001$). There were 15 (5%) bladder perforations in the retropubic sling group and none in the transobturator group, whereas vaginal perforations were more common with the transobturator sling (4.3% vs. 2%, transobturator vs. retropubic sling, respectively). Voiding dysfunction requiring surgery, use of catheter, or both were seen in 2.7% in women who had the retropubic sling versus none of the women who had a transobturator sling ($p = 0.004$). Neurologic symptoms were more common in the transobturator sling (9.4% vs. 4%, transobturator vs. retropubic sling, $p = 0.01$). Among 68% of women with 5-year follow-up, treatment success at 5 years was 7.9% greater after retropubic compared to transobturator sling (51.3% vs. 43.4%, 95% CI −1.4, 17.2); however, a greater proportion of women in the transobturator group reported they were "very much better" or "much better" at 5 years (88% vs. 77%, $P = 0.01$) (Kenton et al. 2015).

Results from a recent meta-analysis of 17 studies involving 2,995 women (Seklehner et al. 2015) are shown in Table 1. Both the objective and subjective cures were slightly better for the retropubic approach. Bladder perforation and excess bleeding were also more common with the retropubic approach. However, neurologic symptoms were more commonly seen in the transobturator sling. Operative time was about 5 min longer in the retropubic approach; however, the authors attribute that to the fact that most of the studies used the original Gynecare TVT sling, which required two separate cystoscopy evaluations, while most currently utilized retropubic sling kits require only one cystoscopy after passing the needles on both sides.

In contrast, the Cochrane working group included 81 trials that evaluated 12,113 women;

Table 1 Outcome of retropubic and transobturator mid-urethral sling

	Retropubic	Transobturator	Odds ratio
Objective cure	86.8%	83.4%	1.35 (95% CI 1.10–1.67, $p = 0.005$)
Subjective cure	76.4%	72.9%	1.24 (95% CI 1.04–1.49, $p = 0.02$)
Bladder perforation	3.2%	0.2%	5.72 (95% CI 2.94–11.12, $p < 0.0001$)
Excess bleeding	3.2%	1.1%	2.65 (95% CI 1.54–4.59, $p = 0.0005$)
Vaginal perforation	0.9%	3.6%	0.29 (95% CI 0.15–0.56, $p = 0.0002$)
Neurological symptoms	3.5%	9.4%	0.35 (95% CI 0.25–0.5, $p < 0.0001$)
Mesh exposure	2.5%	2.6%	0.97 (95% CI 0.63–1.48, $p = 0.97$)
Infection	6.6%	5.4%	1.21 (95% CI 0.79–1.57, $p = 0.28$)
LUTS	9.7%	8.9%	1.04 (95% CI 0.72–1.5, $p = 0.83$)
Urinary retention	6.3%	4%	1.54 ($p = 0.07$) (95% CI not given)
Operative time (min)	28.3	23.4	1.38 (95% CI0.88–1.89, $p < 0.0001$)

LUTS lower urinary tract symptoms (Seklehner et al. 2015)

55 trials with 8,652 women compared the retropubic to the transobturator sling (Ford et al. 2015). The short-term (up to 1 year) subjective cure rates were similar, ranging from 62 to 98% for the transobturator and 71 to 97% for the retropubic sling, respectively (RR 0.98, 95% CI 0.96–1.00; 36 trials, 5,514 women). Short-term objective cure rates were also similar (RR 0.98, 95% CI 0.96–1.00; 40 trials, 6,145 women). In the long term, subjective cure rates ranged from 43% to 92% in the transobturator group and from 51% to 88% in the retropubic group.

The rate of bladder perforation was lower with the transobturator sling (0.6% vs. 4.5%; RR 0.13, 95% CI 0.08–0.20; 40 trials, 6,372 women), and postoperative voiding dysfunction was less common after the transobturator sling (RR 0.53, 95% CI 0.43–0.65; 37 trials, 6,200 women).

The Cochrane working group found that the rate of groin pain postoperatively was higher with the transobturator sling (6.4% vs. 1.3%; RR 4.12, 95% CI 2.71–6.27; 18 trials, 3,221 women), while suprapubic pain was lower with the transobturator sling (0.8% vs. 2.9%; RR 0.29, 95% CI 0.11–0.78). The overall rate of vaginal tape exposure or extrusion was not significantly different between the two approaches – 2.4% with the transobturator sling and 2.1% for the retropubic sling (RR 1.13, 95% CI 0.78–1.65; 31 trials, 4,743 women).

The TOMUS trial (Richter et al. 2010) found no significant difference in success rate between transobturator and retropubic slings when they looked at women with lower Valsalva leak point pressure or maximal urethral closure pressure values. However, several studies have noted a higher failure rate in these women. In a retrospective cohort analysis, a cutoff point of 42 cm H_2O for preoperative maximum urethral closure pressure was identified as predictor of success (Miller et al. 2006). The relative risk of postoperative urodynamic stress incontinence 3 months after surgery in women with a preoperative maximum urethral closure pressure (MUCP) of 42 cm or less H_2O was 5.89 (1.02–33.90, 95% confidence interval) when the transobturator sling was compared with the retropubic sling (Miller et al. 2006). Schierlitz and colleagues performed a randomized controlled trial comparing the transobturator sling to the retropubic sling in women with stress urinary incontinence and intrinsic sphincter deficiency, which was defined as either a maximum urethral closure pressure of 20 cm H_2O or less or a pressure rise from baseline required to cause incontinence (Δ Valsalva or cough leak point pressure) of 60 cm H_2O or less (Schierlitz et al. 2008). Of the 138 women who had follow-up urodynamics at 6 months after surgery, 14 of 67 (21%) in the retropubic sling group had stress incontinence demonstrated during repeat urodynamic assessment compared with 32 of 71 (45%) in the transobturator sling group ($p = 0.004$). Nine of 67 women (13%) in the transobturator sling group requested further surgical treatment to correct SUI compared with 0 of 71 (0%) in the retropubic group. The retropubic

sling appears to be more effective in women with stress incontinence with low MUCP or leak point pressures.

11 Voiding Dysfunction After Mid-urethral Sling

The rate of voiding dysfunction, incomplete bladder emptying, elevated post-void residuals, or difficulty emptying the bladder is generally low after the mid-urethral sling and is reported in about 4% of women (Glavind and Shim 2015; Klutke et al. 2001; Moore and Paraiso 2005; Ozel et al. 2004). The sling can be released in the early postoperative period (within 3 weeks) with successful resolution of voiding dysfunction and with the majority of women maintaining continence (Glavind and Shim 2015; Price et al. 2009). To release the sling in the early postop period, before tissue fibrosis has fully taken place, the anterior vaginal incision can be opened by releasing the sutures and the sling identified and pulled down with gentle traction. Ideally this should be done between 7 and 14 days after surgery if the patient has persistent difficulty emptying the bladder, incomplete emptying, or elevated post-void residual volume. If the sling is not released in the early postop period, sling transection can be very successful in treating voiding dysfunction, but with recurrent incontinence rates as high as 60% (Viereck et al. 2013). Simple division or incision of the sling carries lower risk of recurrent stress incontinence (Agnew et al. 2012; Rardin et al. 2002). The simplest way to incise the sling is to make a vaginal incision in the midline along the anterior vaginal wall and then dissecting to one side or the other. The sling can be easily identified lateral to the urethra with less risk of urethral injury (Long et al. 2004). The sling can then be transected. Early transection (within 1 year of surgery) appears to result in greater improvement in lower urinary tract symptoms than delayed transection (South et al. 2009).

12 Laparoscopic Retropubic Colposuspension (Burch)

12.1 Technique

As in any laparoscopic procedure, it is important that the open procedure is closely mimicked without significant modification in technique. The use of mesh and staple modification of the colposuspension has been shown to be significantly less effective than the open Burch or the laparoscopic Burch using sutures (Ankardal et al. 2005). The retropubic space can be approached via an extraperitoneal or intraperitoneal dissection. The extraperitoneal approach is generally reserved for women who do not require other intraperitoneal procedures. The presence of prior pelvic incisions, especially a low transverse incision, may also hinder the ability to utilize this approach. The advantage of the extraperitoneal approach is that it avoids the risk of intra-abdominal injury and intraperitoneal adhesions. In the extraperitoneal approach, the space of Retzius can be easily dissected with a balloon or with a finger and pneumodissection. However, there is a risk of increased absorption of CO_2 leading to pneumothorax. For the intraperitoneal approach, the bladder is retrograde filled to about 300 ml of normal saline with or without methylene blue to facilitate identification of the bladder. The anterior peritoneum is then incised, and sharp and blunt dissection is used to enter the space of Retzius. The bladder is drained. Two number 0 braided delayed absorbable sutures (such as Vicryl; Ethicon Endosurgery, Inc., Cincinnati, OH) on a CT-2 needle are passed through the endopelvic fascia/vaginal wall about 2 cm lateral to the urethra and bladder, one at the level of the bladder neck and one at the level of the mid-urethra; these stitches are then passed through Cooper's ligament on the ipsilateral side (Tanagho modification) (Tanagho 1976). A figure-of-eight suture can be used to ensure that a good purchase of tissue has been obtained. Some authors place a third stitch on each side. The knots are tied extracorporeally with a hand in the vagina used to elevate the anterior vaginal wall. Gel foam

can be placed between the sutures to promote fibrosis and improve hemostasis. Some authors prefer the use of permanent sutures such as number 0 braided polyester suture (Ethibond, Ethicon Endosurgery, Inc., Cincinnati, OH) rather than the traditional delayed absorbable suture. Cystourethroscopy with a 70° rigid cystoscope is mandatory to confirm integrity of the bladder wall and ureteral patency. The peritoneal defects are then closed sequentially using 2-0 polyglactin 910 sutures (Vicryl; Ethicon Endosurgery, Inc., Cincinnati, OH) in a figure-of-eight intracorporeal surgical slipknot technique.

13 Laparoscopic Burch Compared to Open Burch

The laparoscopic Burch appears to have similar efficacy with the open Burch colposuspension, but there are no long-term studies. Carey and colleagues compared the laparoscopic Burch to the open Burch in a randomized trial of 200 women with urodynamic stress incontinence with maximum urethral closure pressure greater than or equal to 20 cm H_2O (Carey et al. 2006). Operating time was significantly shorter in the open Burch group compared to the laparoscopic Burch group (42 min vs. 87 min, $p < 0.0001$). Estimated blood loss was significantly greater in the open Burch group compared to the laparoscopic Burch group (170 ml vs. 126 ml, $p = 0.03$). Urodynamic stress incontinence at 6 months of follow-up was found in 22% of women in the open Burch group and 28% in the laparoscopic Burch group ($p = 0.22$). At 24 months of follow-up, 30% of the open Burch group and 37% of the laparoscopic Burch group reported occasional or frequent stress incontinence symptoms ($p = 0.38$).

In the Cochrane review of open Burch versus the laparoscopic Burch, no significant differences in subjective and objective cure rate was found (Lapitan et al. 2009). The meta-analyses of data available at less than 1 year (RR 0.98, 95% CI 0.80–1.20) and between 1 and 5 years (RR 0.91, 95% CI 0.77–1.06) did not show any significant differences in subjective incontinence rates between the two groups. When looking at objective outcomes, there was again no significant difference at less than 1 year (RR 0.87, 95% CI 0.62–1.21) and between 1 and 5 years (RR 0.91, 95% CI 0.77–1.06).

14 Laparoscopic Burch Compared to Mid-urethral Sling

When compared to the mid-urethral sling, the laparoscopic Burch again shows comparable efficacy, but long-term outcome data is limited. When the laparoscopic Burch was compared to the mid-urethral sling in the Cochrane review (Dean et al. 2006), there was no statistically significant difference in the reported subjective cure rates between laparoscopic colposuspension and mid-urethral sling procedures within 18 months (RR 0.91, 95% CI 0.80–1.02). This finding remained at longer-term follow-up (4–8 years); the TVT had similar subjective cure rates as laparoscopic colposuspension (RR 1.18, 95% CI 0.36–3.81). However, laparoscopic colposuspension procedures had statistically significantly lower objective cure rates (RR 0.88, 95% CI 0.81–0.95), but there was a wide variety of definitions used for objective cure rate. Urodynamic testing was used to assess objective cure in three studies and showed no difference between the two procedures (RR 0.91, 95% CI 0.80–1.03). There was no difference in the perioperative complication rates between laparoscopic colposuspension and mid-urethral sling procedures (RR 0.99, 95% CI 0.60–1.64). However, laparoscopic surgery took significantly longer than the mid-urethral sling surgery, by an average of 20 min (mean difference 20.31 min, 95% CI 16.75–23.86).

Paraiso and colleagues performed a randomized controlled trial comparing the laparoscopic Burch colposuspension to the TVT (Paraiso et al. 2004). Women with urodynamic stress incontinence with abdominal leak point pressure greater than or equal to 60 cm H_2O and urethral hypermobility were included. The primary outcome was objective cure defined as no leakage during postoperative urodynamic studies. Seventy-two

women were randomized. There was a higher rate of urodynamic stress incontinence at 1-year follow-up in the laparoscopic Burch group compared to the TVT group (18.8% vs. 3.2%; RR 1.19, 95% CI 1.00–1.42, $p = 0.056$). The laparoscopic Burch group had significantly longer operating time (101 min vs. 42 min for laparoscopic Burch vs. TVT sling, $p < 0.001$). However, at longer-term follow-up, in which 74% of the participants were seen at least 4 years after surgery, 58% of the laparoscopic Burch group and 48% of the TVT group reported any urinary incontinence after surgery (RR 1.19; 95% CI 0.71–2.00).

15 Conclusion

Several minimally invasive surgical options exist for women who have failed conservative therapy for stress urinary incontinence.

16 Cross-References

▶ Urinary Incontinence: Diagnosis, Treatment, Avoiding Complications

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Common Problems in Adolescent Medicine

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Abstract

Adolescence is a time of much change and growth. Though exciting, it can present as a challenging time for the youth as well as for her health-care provider. Adolescence begins with puberty; in addition to experiencing many physical changes, the adolescent patient also undergoes numerous ongoing mental and psychosocial changes as she transitions to adulthood. While it is expected that adolescence is the healthiest time in an individual's life, many common medical problems can arise during this time, especially with respect to sexual and reproductive health. These include abnormal menstruation, need for effective and confidential contraception, sexually transmitted infections, and intimate partner violence.

Keywords

Adolescent development • Confidentiality • Consent • HEADSS exam • Sexual development • Abnormal menstruation • Polycystic ovary syndrome • Contraceptive counseling • Sexually transmitted infections • Intimate partner violence

1 Introduction

The care of the adolescent patient can be an overwhelming endeavor for providers who do not routinely work with this complex and interesting age group. Adolescence is a time of much growth and development, both physically and mentally, which makes caring for this age group at times perplexing, yet always rewarding. This chapter will discuss some of the more common concerns that arise when caring for the adolescent patient, from the expected elements of psychosocial and physical development to medical conditions and abnormalities. Furthermore, this chapter includes several resources and tools that providers can utilize when caring for the adolescent patient. As adolescent medicine encompasses a wide variety of disorders, this chapter will not address all aspects of adolescent health. Specifically, this chapter will not review certain conditions that providers may receive referrals for, such as pelvic pain due to mittelschmerz or ovarian cysts, ovarian torsion, uterine fibroids, and teen pregnancy. Providers can refer to "Cross-References" at the end of this chapter for recommended chapters within this text for further information on other conditions that affect adolescents, such as dysmenorrhea, premenstrual syndrome, acute and chronic pelvic pain, contraception and family planning, and congenital anomalies.

2 Consent

The ability to consent to care is a concern that arises commonly in the care of adolescents. Patients who are 18 years or older can consent to care independently, whereas those under age 18 years require parental consent for most aspects of their medical care. However, there are several legal exceptions by which minors can consent to care without parental involvement. The most common exceptions allow minors to legally consent to sensitive health-care services, including sexual and reproductive health care, mental health services, and alcohol and substance abuse treatment. Sexual and reproductive health care encompasses contraception, pregnancy-related care, and examination and treatment after sexual assault. The age of minor consent varies by state and individual treatment type, but in many states, minors 12 and older may consent to sexual health services (Guttmacher Institute 2015).

Providers should be familiar with the local laws pertaining to minor consent. Providers must be aware that the legal considerations for abortion services are not governed by the same laws as are other sensitive services. Most states require parental involvement for the minor seeking abortion services, and this varies from notification of one or both parents to obtaining parental consent to the procedure. Of note, Connecticut, Maine, and the District of Columbia do not have laws pertaining to abortion services for minors, and though parental consent or notification laws have been passed

in California, Montana, Nevada, New Jersey, and New Mexico, those laws have been either temporarily or permanently enjoined by court order and are therefore not in effect. Providers practicing in states without minor consent laws for particular services often obtain patient consent for the service if the minor is mature and able to provide consent. The Guttmacher Institute website is a useful resource that contains up-to-date information regarding minor consent laws across the United States (Guttmacher Institute 2015; Emans et al. 2005).

Throughout the United States, minors may consent for care based on their status and based on local or state laws. Few aspects of minor consent are governed by federal laws, with one exception pertaining to services funded by Medicaid or by the Title X Family Planning Program (English et al. 2010). This most often applies to minors who are seeking care for pregnancy. Additionally minors who are married, minors enlisted in the military, and minors who are financially independent of their parents and living on their own or are otherwise legally emancipated by a court, all commonly referred to as "emancipated minors," are able to consent to their own care, although the legal definition of this term varies by state. Legally emancipated minors can consent to any aspect of their care. Conditions that adolescents, emancipated or not, may otherwise consent to include pregnancy, communicable diseases of public health concern (such as sexually transmitted infections, including human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)), and substance dependence (drugs or alcohol) (Emans et al. 2005). Parenting minors may be able to consent for their child, their own care, or both, but this varies by state as well, and providers should be familiar with local laws.

In addition to considerations pertaining to legal status, providers often utilize the "mature minor" doctrine (alternately, "self-sufficient minor") in obtaining consent from and providing care to adolescents. This doctrine is generally favorable or accepted in many courts across the United States, including some Supreme Court cases pertaining to adolescents. The courts find that "a physician is not liable for providing care without parental consent when the care is within the mainstream of medical opinion, is not high risk, and is provided in a non-negligent manner, as long as the minor is an older adolescent who is capable of giving informed consent to the care and does consent" (English et al. 2010).

> The concept of informed consent is of great import with patients of any age. The ability to provide informed consent must be assessed by the medical provider by taking into account the procedure or treatment at hand, the minor's ability to understand the benefits and complications of the procedure or treatment as explained by the provider, and the minor's ability to understand the implications and/or outcomes of the procedure or treatment.

For sensitive services such as those described above to which minors may consent, providers must also respect patient confidentiality. In most states, information related to such conditions, intervention, and related results or outcomes cannot legally be shared with the minor's parent (s) unless permitted by the minor and documented in their record. In the United States, as discussed above, the laws vary by state, and most states have variable limitations in types of services that minors can consent to, but also variable ages at which minors can give consent. The Guttmacher Institute provides up-to-date, state-specific information on the legal limits pertaining to the whole spectrum of sensitive services (this information can be accessed via www.guttmacher.org) (Emans et al. 2005; Neinstein et al. 2008).

3 Confidentiality

Confidentiality is a common concern that the majority of minors have when seeking care.

Confidentiality pertains to the control of information held in the patient's medical record and whether information from the medical record can be shared with other providers, parents/guardians, or schools, etc. For the most part, minors who seek sensitive services are ensured confidentiality; their medical information cannot legally be shared with any other entity unless the minor signs a release of information (Ford et al. 2004; Neinstein et al. 2008; The Center for Adolescent Health and the Law 2005). Adolescents, often unaware of their rights to confidentiality around such issues, are, as a general rule, hesitant to share sensitive information with their providers, especially at their initial visit. This hesitation can be managed by clearly and explicitly discussing confidentiality and its limits with the minor. Holding such discussions *early* in the patient-provider relationship helps to build rapport and gain the adolescent's trust, minor or not. Providers should also take time to encourage adolescents to include their parents in their care, and providers can assist by acting as a moderator for sensitive discussions. The situations that cross the limits of confidentiality generally include (1) if the adolescent is at risk of harming herself, (2) if the adolescent may harm others, and/or (3) if the provider suspects, or the adolescent discloses, sexual or physical abuse or neglect which requires legal reporting to child protective services. It is recommended that providers preemptively inform the adolescent that if confidentiality must be breached, the adolescent will be informed prior to releasing any information to their parents or the authorities. Such reporting laws also vary by state in their scope and detail, particularly with respect to minor sexual activity, and providers caring for adolescents should be familiar with their local laws and reporting agencies (Ford et al. 2004; Neinstein et al. 2008; The Center for Adolescent Health and the Law 2005).

4 Access to Care for Adolescents

Access to health-care services for adolescents and young adults is not always easy or possible. There are many barriers to care that affect this age group including financial difficulties, lack of or poor access to public transportation, inability to access care due to clinic hours coinciding with school hours, inability to make phone calls to clinics to schedule appointments, and inability to return for follow-up appointments (Advocates for Youth 2015).

These are only some of the many barriers to health care that adolescents cite and each one affects an individual differently, depending on her ethnicity, what community or city she lives in, her socioeconomic status, and so on.

Provider awareness of such barriers allows for accommodations to ease access to care for this vulnerable population. Clinics can offer extended office hours, dedicated adolescent help-line numbers, or vouchers or tokens for public transportation for patients in need (Advocates for Youth 2015). Furthermore, because they face so many barriers to care, adolescents seek out and benefit from low- or no-cost care with an integrated-service approach, where they can have all of their health-care needs met without having to travel between locations and providers. As previously discussed, privacy, confidentiality, and consent are important for all patients, but are essential to the adolescent patient. Adolescents often forgo seeking medical care because they perceive a lack of these basic health-care constructs (The Centers for Disease Control and Prevention 2013). Providers can also make their offices more adolescent-friendly by posting information

relating to the adolescent population (especially, the office confidentiality policy or information on informed consent) in the waiting room as well as the patient rooms (Banikya-Leaseburg and Garrido-Fishbein 2015).

Adopting a "sex-positive" and culturally competent approach helps to achieve optimal care for adolescents who seek sexual and reproductive health-care services (Banikya-Leaseburg and Garrido-Fishbein 2015). Providers can take a sex-positive approach by asking about the patient's sexual orientation and practices (rather than basing counseling on assumptions) as well as about concerns they have about their sexual health. Providing free condoms in the office is another youth-friendly service that many medical clinics offer (Banikya-Leaseburg et al. 2015). Providers should strive to involve youth in any medical decision-making. This engages the young patient and builds on the patient-provider relationship (The Centers for Disease Control and Prevention 2013; Banikya-Leaseburg and Garrido-Fishbein 2015). When able, providers should encourage the adolescent to engage their parent(s) in their health-related discussions or care. This fosters an improved bond and communication between the patient and her parent(s). In addition, patients who have positive parental involvement have been found to have delayed coitarche, decreased substance abuse, improved self-directed care, decreased rates of mental health diagnoses, and improved school performance (Advocates for Youth 2015).

5 Getting to Know the Adolescent Through the HEADSS Exam

There are many nonclinical aspects of care that can strengthen the adolescent-provider relationship. Some of the basic concepts include taking interest in the adolescent as an individual and including the adolescent's family in her care. Additionally, for a patient who presents with her parents, taking time during the clinical visit to meet privately with the adolescent is also instrumental to the patient-provider relationship. This allows a safe and private space to discuss her lifestyle, answer any "embarrassing" questions, and discuss potential risk factors that may impact her health. The HEADSS exam is an interviewing tool that can be utilized by providers to facilitate such discussions in a nonthreatening way (Goldenring and Rosen 2004). As previously discussed, reviewing confidentiality and its limits with the adolescent (and her family, if they ask) prior to the private interview is recommended (Neinstein et al. 2008).

> The HEADSS exam is a progressive interviewing tool that addresses several psychosocial aspects of everyday adolescent life: home, education, activities, drugs, sex, and suicide. In more recent years, the HEADSS exam has been expanded into the HEEADSSS to include a review of eating habits and safety from injury and violence (Ginsburg and Kinsman 2014).

The interview progresses from less invasive questions regarding the adolescent's homelife to more personal questions about whom the adolescent spends time with and what activities she engages in, thereby building rapport with the adolescent. Once the provider and the adolescent are more comfortable, they can then engage in a discussion about even more sensitive topics, such as sexual identity and orientation, sexual behaviors, and emotional disturbances the adolescent may be experiencing. At times the HEADSS exam may need to be deferred until a follow-up visit, as the provider may need more time to build rapport with the adolescent and the family. In addition, the HEADSS exam can be performed in segments to allow the provider to address the medical reason for the office visit. Unaddressed aspects of the HEADSS exam can be completed at subsequent visits (Neinstein et al. 2008). For a list of sample questions, providers can refer to the article, "Getting into Adolescent Heads: An Essential Update" by Goldenring and Rosen; this article lists sample questions and also categorizes them from essential

to optional to help tailor the provider-adolescent interview (Goldenring and Rosen 2004). An additional resource regarding this and many other psychosocial aspects of adolescent care is the textbook, *Reaching Teens: Strength-Based Communication Strategies to Build Resilience and Support Healthy Adolescent Development* by Ginsburg and Kinsman (2014).

6 Stages of Adolescent Sexual Development

It is important for providers to take into consideration an adolescent's stage of development at the time of the encounter and as they devise their treatment plan. Adolescence is a time of rapid change that affects an individual's overall physical and mental state and growth. There are three commonly referred-to stages of adolescent development: early, middle, and late. These stages occur in parallel with puberty, and, girls are often noted to have signs of psychosocial development earlier than boys.

- The first stage of adolescent sexual development, early adolescence, typically occurs between the ages of 9 and 13 years in girls (11–15 years for boys). This coincides with the beginning of puberty, and the early adolescent becomes quite concerned with the changes occurring in her body (Neinstein et al. 2008). Privacy becomes a major concern at this stage. Early adolescents are just beginning to leave childhood, but continue to be predominantly concrete thinkers; these young adolescents do begin to show some abstract thoughts (Monasterio et al. 2010). During this stage, the adolescent female may begin to show interest in other teens at school and have "crushes" that reflect her sexual orientation, which may come with concerns about parental acceptance for those who show interest in the same sex (ACT for Youth Center for Excellence 2015). Most young adolescents in this stage of development are focused on determining, "Am I normal?" They tend to spend much time exploring their bodies and the changes that have started to occur. Because of this, sexual fantasies and masturbation are common in this stage of development. Sexual intercourse, however, is not common this early on (Kann et al. 2014; Monasterio et al. 2010).
- The second stage of adolescent sexual development, middle adolescence, typically occurs between the ages of 13 and 16 years in girls (15–17 years for boys). The middle adolescent is able to think more abstractly (Neinstein et al. 2008). She is more interested in her appearance, takes a strong interest in her peers' opinions, and is focused on determining, "Am I liked?" During this stage, she is beginning to experiment with relationships and is dating. Sexual activity becomes more common during middle adolescence. Centers for Disease Control and Prevention's (CDC) Youth Risk Behavior Surveillance data shows that slightly fewer than 50 % of 10th graders and slightly more than 50 % of 11th graders are sexually active (Kann et al. 2014). The sexually active adolescent is aware of the risk of pregnancy and/or STI, but typically feels that neither is likely to happen to her. It is important for providers and parents to note that sexual behavior at this stage does not always match sexual orientation (Monasterio et al. 2010).
- The third stage of adolescent sexual development, late adolescence, typically occurs between the ages of 16 and 21 years in girls (17–21 years for boys). The late adolescent is more aware of her identity, both personal and sexual. This adolescent is fully capable of abstract thinking (Neinstein et al. 2008). She is concerned about her future. This adolescent is focused on answering the question, "Am I loved?" She is able to have a trusting relationship, can show mutual respect, and has feelings of love and passion (Monasterio et al. 2010).

7 Pubertal Development

Pubertal development progresses with a typical course in most individuals. This section will focus on normal puberty in females, as a precursor to the subsequent sections on adolescent

gynecology. Abnormal pubertal patterns such as precocious puberty and delayed puberty will not be discussed; for information on these, providers can refer to pediatric or adolescent medicine texts, such as *Nelson's Textbook of Pediatrics* or Neinstein's *Adolescent Health Care: A Practical Guide*.

Many changes occur during puberty, including the development of secondary sex characteristics and the development of reproductive capabilities, as well as physical growth, characterized by changes in body habitus and increase in stature (Kliegman et al. 2016). The initiation of puberty is related to the maturation of the hypothalamic-pituitary-ovarian axis, leading to both increased production of and change in the secretory pattern of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Prior to the initiation of puberty, LH and FSH secretion is pulsatile, mainly occurring during sleep. With puberty, the secretion of LH and FSH becomes more consistent, secondary to positive feedback from increasing levels of the sex steroids, estrogen and testosterone. These increasing estrogen and testosterone (as well as other androgens) levels herald the development of the body's adult form (Neinstein et al. 2008).

Providers often utilize the sexual maturity rating (SMR) scale or Tanner stages to document the progression of puberty. The typical course of puberty in females begins with thelarche, or the appearance of breast buds and subsequent breast development, followed by pubarche or pubic hair development (though in a small subgroup of girls, pubarche precedes thelarche). Menarche, or onset of menses, is the next stage of pubertal development. It typically occurs 2–2.5 years after thelarche at an average age of 12.5 years (range 9–15 years) (Neinstein et al. 2008). Physiologic leukorrhea may be noted prior to menarche. Linear growth is also a part of puberty and accelerates during SMR 2–3 in females; linear growth acceleration typically occurs later in males during SMR 3–4. A peak height velocity of 8–9 cm per year is noted for girls and typically occurs about 6 months prior to menarche (Kliegman et al. 2016). Once menarche occurs, linear growth slows down significantly, and girls are anticipated to have approximately 7.5 cm of linear growth remaining. Other changes that occur during the progression of puberty include growth of the female genital tract and ovaries as well as of the external genitalia, including the labia and clitoris (Neinstein et al. 2008).

The typical initial finding of puberty, thelarche, or breast bud development, commonly occurs around age 11. Variations in age at thelarche have been noted, with age at thelarche decreasing in more recent years. Additionally, racial variations are also noted, with the average age of thelarche occurring for African-American girls at 8.87 years and for Caucasian girls at 9.96 years. Several factors are thought to contribute to the earlier onset of puberty in certain groups, including increased rates of obesity, improvements in nutrition, environmental factors, and hormonal exposures (Neinstein et al. 2008; Kliegman et al. 2016; Emans et al. 2005).

Breast development SMR staging consists of five stages (Fig. 1). Sexual maturity rating stage 1 refers to the preadolescent chest, and SMR 2 describes palpable breast bud development with a slight increase in areolar size. As the breasts continue to develop, there is an increase in the amount of breast tissue and enlargement of the areola, and SMR 3 is characterized by such enlargement without change in breast contour. Sexual maturity rating stage 4 is characterized by a "mound on mound" appearance as the areola and the papilla form a secondary mound. Mature, SMR 5 breasts are characterized by nipples that protrude from the breast and areolae that are part of the breast contour (Neinstein et al. 2008; Kliegman et al. 2016).

Pubic hair development consists of five stages as well (Fig. 2). The preadolescent, SMR 1, has no pubic hair noted on exam. With pubarche, SMR 2 pubic hair is noted and is characterized by few, thin, lightly pigmented hairs that are noted along the medial border of the labia and on the mons pubis. With continued development to SMR 3, the pubic hair becomes darker, begins to curl, and increases in number. In SMR 4, the pubic hair is thick, coarse, and curly and covers the mons pubis. The final stage, SMR 5, is characterized by extension of the pubic hair to the medial thighs (Neinstein et al. 2008; Kliegman et al. 2016).

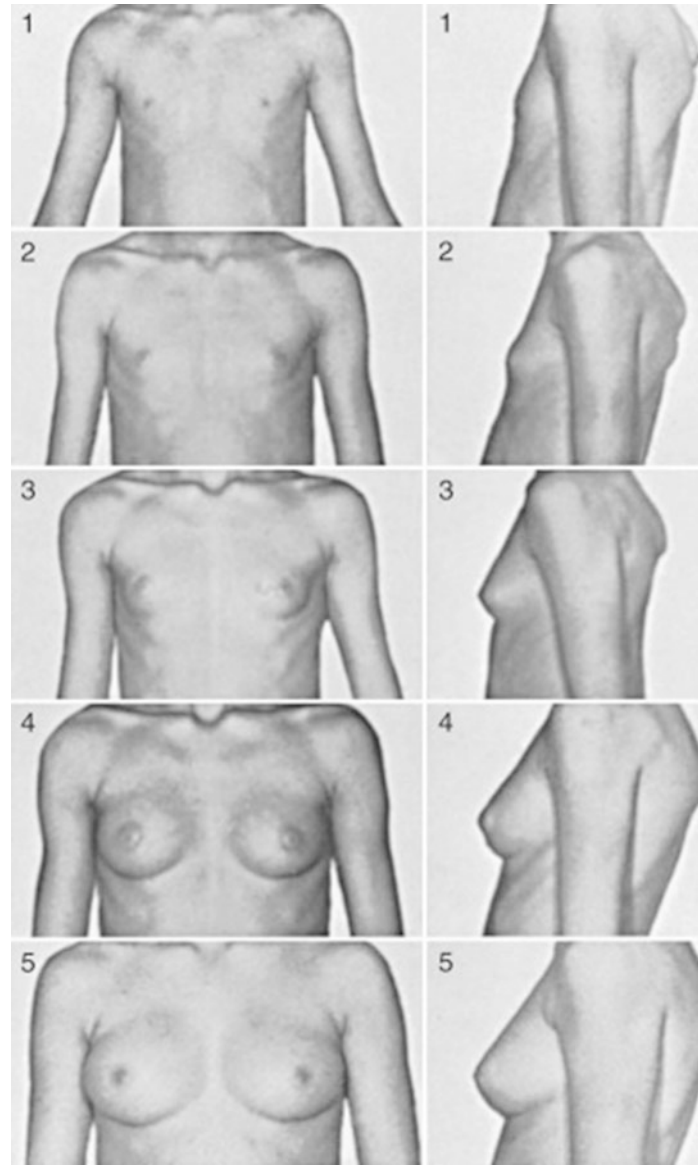

Fig. 1 Sexual maturity ratings of breast changes (Originally published in: Kliegman et al. 2016; with kind permission of © Elsevier, Inc.)

8 Normal Menstruation

Menstrual patterns vary from individual to individual. Many young women are unaware of what constitutes a normal menstrual pattern. Additionally, many young women accept abnormal menstrual patterns as "normal" based on familial patterns, when comparing their own menstrual pattern to that of their mothers, sisters, aunts, etc. From a medical standpoint, the menstrual cycle is considered normal in length if it occurs every 24–38 days. "Frequent menstruation" occurs more often than every 24 days, and "infrequent menstruation" occurs less often than every 38 days (American Congress of Obstetricians and Gynecologists 2014a; Granada et al. 2013).

Young women often present to the medical provider when they note variations in how often they have menses. Even still, many young women become concerned about the regularity of their cycle when they note that, "it always starts on a

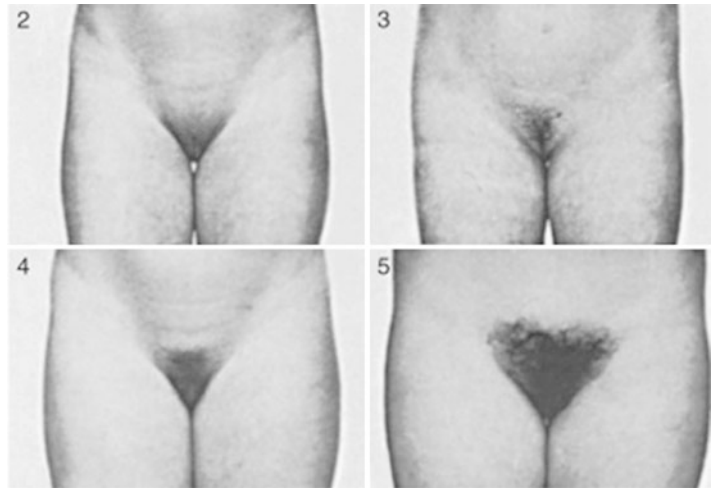

Fig. 2 Sexual maturity ratings of pubic hair changes (Originally published in: Kliegman et al. 2016; with kind permission of © Elsevier, Inc.)

different day." An individual's menstrual pattern can vary widely. Cycle length can increase or decrease by 2–20 days from the start of the previous menses and still be considered a "regular" cycle (American Congress of Obstetricians and Gynecologists 2014; Granada et al. 2013). If a patient's menstrual cycle persistently varies by more than 20 days, she is considered to have irregular menstrual cycles and to warrant investigation. Further, if an adolescent experiences no menstrual bleeding for a 90-day period, it is considered "absent menstrual bleeding," or amenorrhea, and also warrants investigation (American Congress of Obstetricians and Gynecologists 2014b).

Normal duration of menstrual flow is 4.5–8 days (American Congress of Obstetricians and Gynecologists 2014b; Granada et al. 2013). Typically, with normal menses, women experience the heaviest flow on days 1–3. The majority of the uterine content (about 90 %) is expelled in the first 3 days of the menses. Normal menstrual flow requires three to six pads or tampons per day. If menstrual bleeding lasts less than 4.5 days, more specifically no longer than 2 days, this is considered to be shortened menstrual bleeding. Menstrual bleeding lasting more than 8 days is considered prolonged menstrual bleeding, and a diagnosis of abnormal uterine bleeding and related work-up should be considered (American Congress of Obstetricians and Gynecologists 2014a).

9 Specific Patterns of Abnormal Menstruation

There are several patterns of abnormal menstruation that commonly present during adolescence. This section will focus on amenorrhea. Although not an abnormal menstrual pattern, dysmenorrhea is quite common during adolescence and often leads to missed school days and can contribute to difficulty in school performance. Dysmenorrhea is usually primary in nature in this age group. Secondary dysmenorrhea is less common, but endometriosis, which was previously thought to occur only in older women, is found in this age group as well.

Abnormal uterine bleeding (AUB), previously known as dysfunctional uterine bleeding, occurs frequently in this age group. When evaluating a patient with AUB, it is important to thoroughly review the pattern of bleeding the patient is experiencing. In evaluating AUB it is essential to determine whether the heavy and/or prolonged vaginal bleeding is a new occurrence or if it has been present since menarche. If heavy menstrual bleeding has been present since menarche, this may indicate an underlying bleeding diathesis, most commonly von Willebrand disease (American Congress of Obstetricians and Gynecologists 2014a). Table 1 lists other symptoms that support further work-up for bleeding diathesis.

Table 1 Initial screening for underlying bleeding diathesis

History of one or more of the following:	History of two or more of the following:
Postpartum hemorrhage	Increased or easy bruising
Surgery-related bleeding	Petechiae
Bleeding related to dental procedure	Epistaxis
	Hematuria or hematochezia 1–2 times per month
	Frequent gum bleeding
	Family history of bleeding symptoms

Adapted from American Congress of Obstetricians and Gynecologists (2014a)

10 Amenorrhea

Amenorrhea is defined as the absence of menstruation and can be a sign of various underlying conditions. Amenorrhea can be either primary or secondary. Primary amenorrhea is defined as the absence of menses past age 15, in the presence of secondary sexual characteristics. Secondary amenorrhea is the absence of menstruation for 3–6 months in a post-menarchal patient (Neinstein et al. 2008). A thorough history and physical are important in the evaluation of a patient with amenorrhea.

- When obtaining the patient's medical history, a provider should also obtain a detailed menstrual history as well as the menstrual history of close female relatives (Emans et al. 2005).
- It is important to document the patient's course of pubertal development thus far, any history of chronic illness, medication use, history of surgeries, as well as possible treatments for malignancies, endocrine abnormalities, or immunologic conditions.

There are several important aspects of the review of systems to address in patients with amenorrhea.

- These include any history of headaches, visual disturbances, disordered eating, fluctuations in weight, and degree of involvement in sports or exercise and history of acne or hirsutism (Emans et al. 2005).

The exam findings can assist in identifying the underlying cause, whether it is related to hormonal abnormalities originating along the hypothalamic-pituitary-ovarian axis, to a condition that affects the function of the reproductive organs, or to a structural abnormality (Emans et al. 2005).

- The evaluations of the vital signs, height and weight, are useful assessment tools in the evaluation of a patient with amenorrhea. Patients who are underweight may have malnutrition as a consequence of many underlying etiologies, such as neglect or eating disorder; the body mass index (BMI), or the weight in kilograms divided by the square of the height in meters, is an important measurement that can be used in this initial assessment; percentile curves for BMI for girls ages 2–18 have been published by CDC. Short stature and decreased height velocity are often indicators of endocrine abnormality, such as thyroid dysfunction or hypopituitarism; they can also indicate inflammatory bowel disease or other malabsorption syndromes. Signs of Turner syndrome, congenital adrenal hyperplasia, or Cushing syndrome should also be noted (Emans et al. 2005).
- Tanner or SMR staging is necessary for evaluating the presence of secondary sexual characteristics, via breast exam as well as external genital exam (Neinstein et al. 2008; Emans et al. 2005). Compression of breast tissue is recommended to evaluate for galactorrhea, as this may go unnoticed by the patient.
- The external genital exam should include an assessment for clitoromegaly, hymenal

patency, and presence of estrogenization of vaginal tissues. The presence of estrogen leads to pink, moist vaginal mucosa, while estrogen deficiency leads to reddened, thin mucosa. In a patient with normal pubertal development and amenorrhea, imperforate hymen typically presents as a bluish bulging mass on external exam or hematocolpos. Menstrual flow can also be prevented by the presence of a transverse vaginal septum, vaginal agenesis, or other müllerian defects. The bimanual exam with insertion of a single finger for cervical and uterine palpation can assist in evaluation for anatomical abnormalities (see chapter "► Gynecologic History and Examination of the Patient").

– If there is concern for anatomical abnormality, if the examination is technically difficult to perform, or if the patient is too uncomfortable with examination, pelvic ultrasound is a useful adjunct to assess anatomy. Although transvaginal ultrasound may provide more detailed images than transabdominal ultrasound, it is not recommended in pre-coitarchal patients. In addition, patients with poor estrogenization may have small reproductive structures that may be difficult to assess with ultrasound. Should the ultrasound demonstrate an abnormality or be inconclusive, magnetic resonance imaging will provide detailed images of the structures in question (Neinstein et al. 2008; Emans et al. 2005).

Patients with secondary amenorrhea should undergo a similar examination. However, because patients with secondary amenorrhea demonstrated previous menstrual flow, the concern for anatomical abnormalities is low (Emans et al. 2005). The index of suspicion for pregnancy should always be high for patients with secondary amenorrhea, as well as for patients with delayed menarche. In addition to the aforementioned approach to the patient with amenorrhea, the use of a short course of progestin is helpful in assessing for the presence of estrogen and an estrogen-primed uterus in patients with amenorrhea and a negative pregnancy test. The "progestin challenge" is not indicated in patients with pubertal delay or in those with estrogen deficiency. Two progestin regimens commonly used are:

– Medroxyprogesterone 5–10 mg PO once daily for 5–10 days
– Micronized progesterone 200–300 mg PO once daily for 10 days

Bleeding usually occurs 2–3 days after completing the progestin course, but can take up to 10 days to occur. Menstruation in response to progestin challenge indicates normal estrogen levels. Of note, patients with ovarian insufficiency or with prolactinoma may have normal menstrual flow after progestin challenge.

- Estradiol level can be obtained as an adjunct, but levels vary depending on which time in the menstrual cycle the level is drawn, and is therefore less helpful (Emans et al. 2005).

Laboratory tests are often indicated in the work-up for amenorrhea (Emans et al. 2005; Neinstein et al. 2008).

- The initial tests include urine or serum human chorionic gonadotropin (HCG) test, a complete blood count (CBC), urinalysis, thyroid-stimulating hormone (TSH), FSH, and prolactin; these should ideally be drawn prior to starting hormones or progestin challenge.
- In patients in whom chronic illness is the suspected etiology for amenorrhea, the initial diagnostic laboratory work-up should also include sedimentation rate, renal function, electrolyte panel, and celiac panel.
  – The HCG level is recommended for primary and secondary amenorrhea work-up, as, although rare, pregnancy can occur prior to menarche. The FSH level will assist in determining whether ovarian function is intact. High FSH levels (typically >20) indicate ovarian insufficiency. Patients with high FSH level should have a repeat level checked in 2 weeks before ascribing

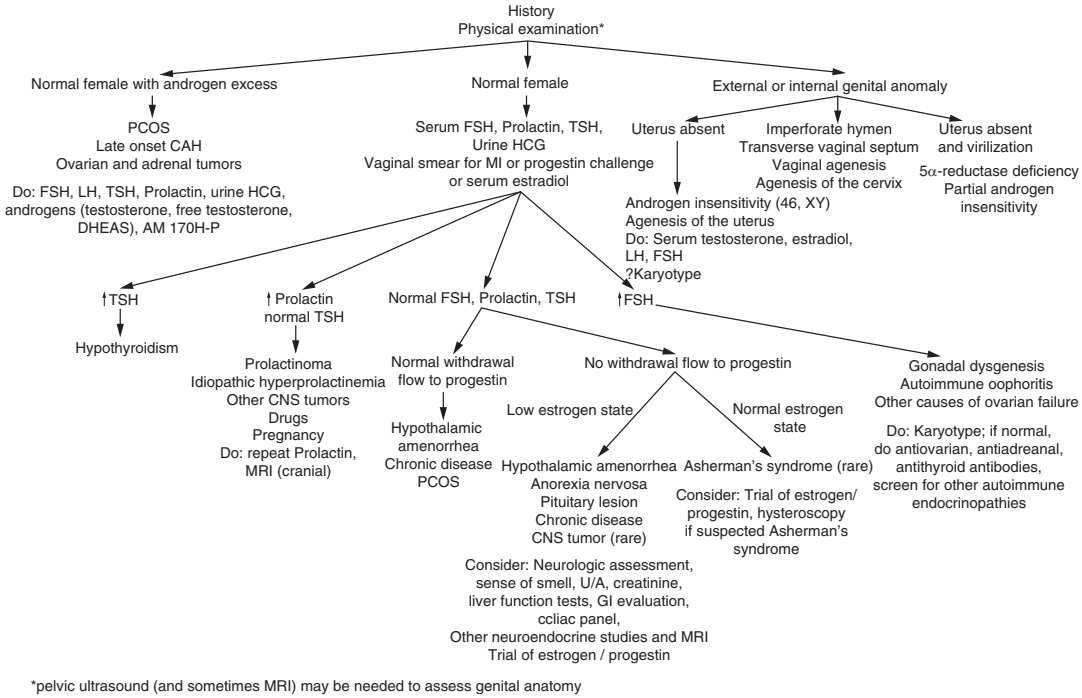

Fig. 3 Summarizes the varied differential for amenorrhea and findings associated with each underlying cause (Originally published in: Emans et al. 2005; with kind permission of © Lippincott Williams & Wilkins)

this diagnosis; repeat level is not necessary in patients known to have received chemotherapy or radiation. Low or normal FSH levels indicate primary hypothalamic dysfunction or hypothalamic dysfunction that is related to chronic illness, endocrine abnormality, eating disorder, stress, or a central nervous system tumor (Emans et al. 2005; Neinstein et al. 2008) (Fig. 3).

11 Eating Disorders and Disordered Eating in the Adolescents

Disordered eating patterns are common among women of all ages and can go unnoticed by health-care providers. Disordered eating can progress to eating disorders as defined by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), including anorexia nervosa, other restrictive eating patterns, and bulimia nervosa, all of which may lead to oligomenorrhea or amenorrhea. In early adolescence, girls are frequently preoccupied with the appearance of their bodies, especially when compared to their peers; when extreme, this can manifest as an eating disorder. This is also an issue for older teenagers, secondary to anxiety related to separation from their family or support system, and decision-making around career, life goals, etc. (Emans et al. 2005).

> Providers should keep a high index of suspicion for eating disorders in young women with menstrual abnormalities, even in patients with normal body mass indexes, but noted weight loss (Golden et al. 2003).

In addition, providers should be aware of the changes made to the diagnostic criteria of several eating disorders with the publication of the DSM-5. This discussion will focus on the changes

related to diagnosis of anorexia nervosa, as those related to the other eating disorders are minor. It is recommended that providers become familiar with the DSM-5 diagnostic criteria, as the diagnosis of an eating disorder can be made with more certainty with the new criteria, and early diagnosis brings hope of appropriate treatment sooner for these patients.

Anorexia nervosa (AN) is characterized by significant fear of gaining weight or becoming fat (American Psychiatric Association 2013). It occurs often in young women and leads to abnormal perception of their body habitus. This leads to difficulty in employing healthy eating habits and often manifesting as either persistent restriction of intake or binging with purging in order to maintain low weight and to prevent weight gain (American Psychiatric Association 2013). The physical manifestations of AN include malnutrition, cachexia, dry skin with poor integrity, hair loss, thyroid dysfunction, cardiac arrhythmia (most often bradycardia), gastrointestinal dysmotility, constipation, dehydration, electrolyte abnormalities, and, classically, amenorrhea (Rosen 2010; Golden et al. 2003). The DSM-5 removed amenorrhea from the diagnostic criteria for AN for several reasons. First, this criterion was removed to be more inclusive of male patients, as AN has been increasingly recognized in males. Additionally, the diagnosis of AN can be made in premenarchal girls as well as in women using oral contraceptives, which can be used to either induce menses in those with low body mass index or to skip menses with extended cycle dosing. Furthermore, some patients with AN continue to menstruate despite rapid weight loss or low body mass (American Psychiatric Association 2013). The data on the effect of hormone replacement in the treatment of eating disorders is scant and does not provide much clarity.

The use of hormone replacement for the osteopenia associated with eating disorders has been shown to lead to premature closure of the adolescent growth plates and growth arrest (Golden et al. 2003).

Additionally, the use of hormonal contraceptives for the management of amenorrhea in the context of AN is not recommended by the Society for Adolescent Health and Medicine, as medication-induced monthly menses is counterproductive to the ED treatment plan and falsely reassures patients that they are at a healthy weight (Golden et al. 2003). The best treatment for amenorrhea related to ED or disordered eating, including female athlete triad, is improved nutrition and increase in body mass index.

12 Female Athlete Triad

Although not classified as an eating disorder, the female athlete triad (triad) is an important diagnosis to consider in young female athletes with amenorrhea. The triad is a constellation of findings common to competitive athletes and consists of disordered eating, amenorrhea, and osteoporosis (Drinkwater et al. 2005). It can occur in young women participating in any sport, but is more commonly noted in ballet dancers, gymnasts, and runners. Amenorrhea in the triad is most often caused by hypothalamic hypofunction that occurs as the body redirects energy to maintain essential bodily functions such as cardiac output and blood flow to the brain, in those participating in intense athletic activity and training (Witkop and Warren 2010). Interestingly, the time of onset of sports participation with respect to menarche can be a factor in the development of the triad. Girls who begin athletic training prior to menarche are noted to have a delay in menarche by 5 months for each year of athletic training. Conversely, the rate of amenorrhea is lower for girls

who begin athletic training after menarche (Emans et al. 2005; Nattiv et al. 2007).

At-risk athletes develop a preoccupation with improving their performance and often employ disordered eating patterns to decrease their body mass or body fat. Disordered eating can be the result of restrictive eating by means of a frank eating disorder, such as AN or bulimia nervosa, or by periodic purging, binging, fasting, or subclinical eating (dieting) (Emans et al. 2005). Alternatively, athletes can increase their energy expenditure to achieve weight loss by increasing the intensity of their training regimen without increasing nutritional intake (Drinkwater et al. 2005). Although weight loss can be intentional, often adolescent athletes develop the triad unintentionally as they are unaware of the need for increased intake to support their metabolic needs while training for sports; typically, their intake would be sufficient for an adolescent who does not engage in sports.

- Providers can assist athletes in preventing or reversing this effect by reviewing nutritional recommendations to maintain healthy weight and to prevent energy deficits in those with intensive training regimens (Nattiv et al. 2007; Drinkwater et al. 2005).

As previously discussed, pubertal changes are also associated with increase in vertical growth and height (Neinstein et al. 2008). This growth is supported by good nutrition, including adequate protein intake, as well as various other nutrients (Kliegman et al. 2016). The nutrients that are important to bone growth are calcium and vitamin D; estrogen also plays a large role in bone growth (Witkop and Warren 2010). In addition to lower-than-expected BMI, poor nutrition in the triad leads to osteopenia or osteoporosis, increasing the risk for and incidence of stress fractures (Nattiv et al. 2007).

- Providers should have a high index of suspicion for osteopenia and should consider evaluating bone mineral density (BMD) with dual energy X-ray absorptiometry scan or equivalent method in order to make recommendations regarding bone health in the adolescent athlete with amenorrhea (Emans et al. 2005).
  - As expected, risk of osteoporosis can be decreased with adequate intake of calcium and vitamin D (Nattiv et al. 2007). Improved body weight with good nutrition leads to increased bone formation. Additionally, bone resorption decreases once the adolescent notes return of regular menstruation, which is also achieved with good nutrition (Witkop and Warren 2010). Because these young women experience a period of poor bone growth, the reversal in BMD after treatment remains below average when compared to healthy peers in the long term (Drinkwater et al. 2005).

13 PCOS in the Adolescent

In more recent years, increasing rates of obesity have highlighted metabolic changes in adolescents that often lead to secondary amenorrhea and increased consideration of polycystic ovary syndrome (PCOS) as an underlying diagnosis (Auble et al. 2013). However, there is much controversy with respect to ascribing this diagnosis to adolescents. The current diagnostic criteria outlined by Rotterdam, the National Institute of Health, and the Androgen Excess Society cannot be applied to adolescents. The reason for the controversy is multifactorial. During adolescence, and more specifically, during puberty, an individual typically undergoes many normal changes that may be confused with PCOS. This can lead to either overdiagnosis of PCOS in patients experiencing natural fluctuations in function that occur with puberty or underdiagnosis of PCOS in patients who are thought to be experiencing puberty-related changes well after the usual timeline of events (Auble et al. 2013).

Amenorrhea, oligomenorrhea, and other patterns of irregular menstruation secondary to anovulatory cycles are common in the first few years after menarche (Hardy and Norman 2013).

Another confounder that complicates PCOS diagnosis is obesity, which often leads to anovulatory cycles in this age group. The majority of young women, about 95 %, have regular menstrual cycles (see definitions under section "8") once they reach a gynecologic age of 3 years (gynecologic age = current age – age of menarche). This information may be helpful in diagnosing PCOS more accurately by restricting its application to young women who have a higher gynecologic age, thereby removing normal postmenarchal menstrual variability as a confounder (Hardy and Norman 2013).

An ultrasound of the ovaries is often obtained in an effort to diagnose PCOS in adult women (Auble et al. 2013; Hardy and Norman 2013). However, a polycystic appearance of the ovary on ultrasound is common during adolescence. Ovarian volume increases with menarche, as does the antral follicle count, leading to a "polycystic appearance" when visualized by ultrasound. These changes persist for some time after menarche, and the size of the ovaries and the number of antral follicles slowly decrease as a woman ages.

Therefore, while ultrasound for identification of "polycystic ovaries" may be more useful for diagnosis of PCOS in older women, it is generally not indicated in adolescents (Auble et al. 2013; Hardy and Norman 2013).

Hyperandrogenism typically manifests as acne, hirsutism, hair loss, and/or male pattern baldness (Hardy and Norman 2013). Regarding hirsutism, it is important to take into account the patient's ethnic background, as well as familial patterns of hair growth. The Ferriman-Gallwey score (see graphic in chapter "▶ Workup and Management of Polycystic Ovary Syndrome") is typically used to grade the degree of hirsutism across different areas of the body; however, this tool was validated in use for Caucasian women and may not be applicable to patients from other ethnic backgrounds. Evaluation for hyperandrogenism involves clinical exam as well as assessing for elevated serum androgen levels, including free and total testosterone and dehydroepiandrosterone sulfate (DHEAS) and, in some cases, 17-beta-OH-progesterone and androstenedione. Documented evidence of hyperandrogenemia is the "most useful diagnostic feature in adolescents given that menstrual irregularity, ovarian morphology and clinical hyperandrogenism do not correlate strongly with PCOS in this population" (Hardy and Norman 2013).

Obesity can complicate some of the relevant natural changes seen in puberty. Hormonal abnormalities seen in early puberty can persist past puberty in patients, leading to increased peripheral estrogen production and menstrual abnormalities (Kansra and Menon 2013; Khan 2007). In addition, obesity often leads to hyperinsulinism and insulin resistance, which may manifest as acanthosis nigricans. Insulin is a hormone with gonadotropic effect that synergizes LH activity. Thereby, hyperinsulinism can disturb normal ovarian function, lead to menstrual abnormalities, and disrupt fertility. In addition, hyperinsulinism decreases hepatic production of sex hormone-binding globulin, resulting in increased free testosterone levels, again manifesting in signs of hyperandrogenism such as acne and hirsutism, and altering menstruation (Kansra and Menon 2013; Khan 2007).

Although diagnosis can be difficult in this age group, providers continue to diagnose and treat PCOS or adolescents "at risk for PCOS" in an effort to decrease the long-term risk of cardiovascular morbidity and mortality secondary to comorbid conditions such as insulin resistance, type

2 diabetes mellitus, dyslipidemia, metabolic syndrome, cardiovascular disease, and endometrial cancer (Auble et al. 2013; Hardy and Norman 2013; Kansra and Menon 2013). Treatment modalities utilized by providers include weight management through lifestyle modification, contraceptives, antiandrogens, and/or metformin. Other special considerations in the adolescent population include increased rates of poor self-image, cosmetic issues, and the impact of these on the development of depression and anxiety in patients diagnosed with PCOS. As with older patients, adolescents with PCOS are also concerned with the effect of their diagnosis on their fertility, even though they may not be seeking pregnancy in the near future. In addition to counseling patients related to its diagnosis and treatment, providers should take time to counsel adolescents with or at risk for PCOS about comorbid conditions and related outcomes (Auble et al. 2013; Hardy and Norman 2013; Kansra and Menon 2013).

14 Adolescent Sexuality

Sexuality is a complex construct. It is a manifestation of the physical development and emotional maturation noted during puberty and encompasses a secure sense of self and the manner in which one interacts with others (ACT for Youth Center for Excellence 2015; Emans et al. 2005). Sexuality and sexual orientation become important as an adolescent completes puberty, but gender identity develops much sooner. Gender identity develops very early in childhood and refers to a person's sense of self as male, female, etc. For the majority of humans, gender identity is aligned with their physical sexual characteristics or genitalia or their gender assigned at birth. For the small subset of people with gender dysphoria, there is a mismatch. Persons who identify as female but were born with male genitalia are termed transgender female. Likewise, transgender male refers to those who identify as male but were born with female genitalia. Although the two are often conflated, gender identity is a basic defining characteristic that is completely independent of sexual orientation. Sexual orientation refers to one's sexual or romantic attraction to others and can manifest as attraction to the opposite gender, same gender, both genders, etc. During adolescence, it is common for youth to experiment with partners from either the same or opposite gender. Such behaviors during adolescence do not predict behaviors, preferences, or identities in adulthood.

- The provider can utilize the HEADSS interview to discuss the adolescent's sexuality and sexual practices, as well as counseling pertaining to all aspects of sexual health; gender identity can also be addressed during the HEADSS exam when it presents as a concern (ACT for Youth Center for Excellence 2015; Emans et al. 2005).

15 Helping Adolescents Choose Effective Contraception

The increased use of contraceptives in the adolescent population has been paramount in decreasing the teen pregnancy rate in the United States (Centers for Disease Control and Prevention 2011). According to the most recent data from the CDC, there has been a 60 % decrease in the overall birthrate between 1991 and 2013 (Centers for Disease Control and Prevention 2015a). Despite this decrease, the United States still has one of the highest teen birthrates among industrialized nations. The vast majority of teen pregnancies are unintended and about one-third end in termination (Centers for Disease Control and Prevention 2015a). Teen pregnancy and teen childbearing cost the US health-care system billions of dollars per year (The National Campaign to Prevent Teen and Unplanned Pregnancy 2015b).

Many medical societies including ACOG and the American Academy of Pediatrics

recommend the use of long-acting, top-tier contraceptive methods for sexually active adolescents (American College of Obstetricians and Gynecologists 2012a; American Academy of Pediatrics 2014).

There are many benefits for the adolescent in using a top-tier contraceptive method. These include highly effective contraception, increased rates of continuation of contraception, the use of a discrete contraceptive method, and greatly increased ease of use (American College of Obstetricians and Gynecologists 2012a; American Academy of Pediatrics 2014). The data from the Contraceptive Choice Project provides evidence that supports the use of long-acting contraceptive methods, as long-term contraceptive use was also associated with lower pregnancy and termination rates. The study demonstrated that when women of all ages were provided with structure contraceptive counseling discussing methods in order of efficacy, women were most likely to choose a top-tier method for contraception (an intrauterine device or the hormonal implant) (Diedrich et al. 2015). In addition, the Contraceptive Choice Project demonstrated that the continuation rate for long-term, top-tier contraceptive methods was significantly higher compared to methods other than the IUDs/implant (Diedrich et al. 2015).

Providers must take into consideration the patient's needs and assist the patient in choosing a method that suits her lifestyle. Providers can utilize the Centers for Disease Control and Prevention's Reproductive Life Plan Tool with adolescent and young adult women, just as with older women (Centers for Disease Control and Prevention 2014). Importantly, asking young women to provide an answer to the question "When do you plan on having your first (or next) child?" often prompts young women to consider contraception. The Adolescent Health Working Group recommends initiating the discussion on contraception by discussing what methods the adolescent patient is aware of and what method she is interested in (Monasterio et al. 2010). When providing contraceptive counseling, CDC and ACOG recommend that providers present the patient with a "menu of options" of contraceptive methods (American College of Obstetricians and Gynecologists 2012a).

- These organizations also recommend discussing contraceptive options from most effective to least effective at preventing pregnancy, including a discussion of their associated benefits and side effects.

The National Campaign to Prevent Teen and Unintended Pregnancy reiterates the above contraceptive counseling recommendations, with additional recommendations collected via focus groups with women of reproductive age to help providers increase utilization of long-acting contraceptive methods (The National Campaign to Prevent Teen and Unplanned Pregnancy 2015a). In addition to reviewing a young woman's reproductive life plan, providers should discuss the patient's needs, concerns, and expectations about the contraceptive methods they are interested in. This is paramount in aiding her to choose the best method for her and should be assessed early in the conversation.

Providers should focus on the hormonal implant and the IUDs first in contraceptive counseling, emphasizing that these methods are "low maintenance" and require no further action by the patient after placement.

It is recommended that providers relay other women's experiences with the methods discussed to provide information on how it will feel for the patient herself, as well as for her partner(s). Discussing the reversibility of the contraceptive method and counseling the patient on when fertility will return with discontinuation of the method are quite important, especially to young women (The National Campaign to Prevent Teen and Unplanned Pregnancy 2015a). Providers are encouraged to refer to the National Campaign's

website for contraceptive counseling tips as well as the chapters in this text which review conceptive methods, for full details regarding use, benefits, contraindications, and side effects.

16 Emergency Contraception

Emergency contraception (EC) is a contraceptive method used to prevent pregnancy after unprotected intercourse.

- Its use is indicated in sexual assault, unprotected vaginal intercourse, and contraceptive failures, including inappropriate use of hormonal contraceptives and barrier method malfunction (Committee on Adolescence 2012; American College of Obstetricians and Gynecologists 2015). Hormonal contraceptive efficacy decreases greatly when oral contraceptive pills are missed for three consecutive days, when the contraceptive patch is off for more than 24 h, or the contraceptive ring is out for more than 3 h.

There are three commonly used forms of EC that can be utilized within 5 days or 120 h of unprotected intercourse: the levonorgestrel tablet, the ulipristal acetate tablet, and the copper IUD (Monasterio et al. 2010; American College of Obstetricians and Gynecologists 2015).

- The levonorgestrel tablet is available under several brand names and is available for use by prescription or over the counter. Levonorgestrel is a progestin that is effective as EC when given as a single 1.5 mg oral dose within 120 h of unprotected intercourse (Committee on Adolescence 2012; American College of Obstetricians and Gynecologists 2015). Levonorgestrel is 98.9 % effective when taken within 72 h of unprotected intercourse. Efficacy decreases somewhat between 72 and 120 h after unprotected intercourse, but studies show it is still effective as EC. The side effects noted with levonorgestrel when used as EC include nausea, vomiting, heavier menstrual bleeding, and spotting (Committee on Adolescence 2012; American College of Obstetricians and Gynecologists 2015).
- Ulipristal acetate is a selective progesterone receptor modulator that prevents follicular development and ovulation (Committee on Adolescence 2012; American College of Obstetricians and Gynecologists 2015). It also decreases the thickness of the endometrial lining and may affect implantation. One dose of ulipristal 30 mg orally within 120 h of unprotected intercourse is just as effective as levonorgestrel as EC. Unlike levonorgestrel, however, ulipristal's efficacy remains high as EC when administered between 72 and 120 h after unprotected intercourse; it also may be used in women with BMI up to 30 kg/m^2, without a decrease in efficacy (American College of Obstetricians and Gynecologists 2015). The most common side effects noted with ulipristal are headache, nausea, and abdominal pain. If vomiting occurs within 3 h of administration, it should be re-dosed. Of note, animal studies have shown fetal loss in the first trimester with ulipristal; however no human data is available. There are no reports of fetal malformation with ulipristal use (Committee on Adolescence 2012; American College of Obstetricians and Gynecologists 2015; Fisher and Lara-Torre 2013).
- The copper IUD can be used for EC in a patient who is seeking EC and is also interested in long-term contraception (Monasterio et al. 2010). Providers should consider the copper IUD for EC in overweight or obese patients, as effectiveness of levonorgestrel may be decreased in overweight (BMI $\geq$25 kg/m^2) or obese (BMI $\geq$30 kg/m^2) patients and the effectiveness of ulipristal acetate may be decreased in obese patients (American College of Obstetricians and Gynecologists 2015). The copper IUD can be placed for EC within 5–7 days of unprotected intercourse and should not be affected by patient weight or BMI. As with routine IUD placement, use is contraindicated in patients with symptoms of cervicitis/PID, current diagnosed sexually transmitted infection (STI), history of STI in the last 3 months,

or at high risk of contracting STI. Please refer to chapter "► Contraception and Family Planning" for more information on IUD placement (Monasterio et al. 2010).

Providers should use visits for EC as an opportunity to discuss the patient's reproductive life plan, to discuss more reliable contraceptive methods, and to screen for sexually transmitted infections. When prescribing EC, providers should counsel patients on the indication, use, and side effects (Committee on Adolescence 2012). In addition, for patients who prefer to use barrier method or are unable to choose more reliable methods of contraception, it is recommended that the provider prescribe EC for immediate use in case of future unprotected intercourse; levonorgestrel is commonly prescribed and covered by most medical insurance. Studies have shown that providing adolescents with advanced prescriptions increases the likelihood of EC use, decreases the rate of teen pregnancy, and does not increase risky sexual behavior (American College of Obstetricians and Gynecologists 2015; Sanfilippo and Lara-Torre 2009).

17 Sexually Transmitted Infections: Special Considerations in Adolescents

The rates of sexually transmitted infections (STIs) in the United States are highest among those ages 15–24 years (Workowski and Bolan 2015). The high prevalence of STIs in this age group is attributable to high-risk sexual behaviors commonly observed in adolescents. Although adolescents often have many sequential short duration sexual relationships, they also may continue to have multiple sexual partners; they may engage in sexual intercourse while under the influence of various substances, and consequently they often have low rates of condom use. The most incident STI in this age group is human papillomavirus (HPV), followed by chlamydia, and then gonorrhea (see chapter on STI for more information). Most often, patients who are symptomatic seek care and obtain treatment. However, because chlamydial infections, and at times gonorrheal infections, are often asymptomatic, they frequently go unnoticed, again increasing the STI burden in this population. For this reason, CDC recommends that asymptomatic adolescents should have chlamydia and gonorrhea screening once a year. Recommended STI screenings for sexually active adolescent females are summarized in the table below. These recommendations are based on CDC recommendations published in the 2015 STI treatment guidelines (Workowski and Bolan 2015). Providers should refer to the chapter on STIs for a full review of symptoms, screening, and management (Table 2).

In addition to high-risk sexual behavior, research has shown that there are several biological and anatomical factors that contribute to the higher rates of STIs in adolescents (Hwang et al. 2009). During puberty, the cervical epithelium undergoes squamous metaplasia by which the columnar epithelial tissue transforms into squamous epithelial tissue. The transformation zone, or ectropion, is visible at the cervical os in early adolescence and becomes less visible with pubertal maturation. The columnar cells of the cervical epithelium are typically the site of infection with chlamydia and gonorrhea. Interestingly, the transformation zone is also the target for HPV infection, as the cells undergo frequent replication and differentiation (Hwang et al. 2009).

During puberty, the vaginal pH shifts from a less acidic to a more acidic pH, less than 4.5 (Moscicki et al. 2001). This physiologic change is thought to trigger squamous metaplasia.

> It is thought that prevention of this pH change delays cervical maturation; one theory is that frequent exposure to alkaline conditions, such as bacterial vaginosis or semen, can lead to delay of cervical maturation and increase risk for STIs.

In addition to pubertal changes, several external factors have been noted to affect cervical

Table 2 Routine STI screening for adolescent females (noted in table already)

Routine STI screening for adolescent females	
Chlamydia trachomatis	Annual screening for all sexually active females <25 years
	More frequent testing (every 3–6 months) for symptomatic patients and for high-risk patients:
	Multiple sexual partners
	STI clinic patients
	Adolescent clinics
	Correctional facilities
Neisseria gonorrhoeae	Annual screening for all sexually active females <25 years
	More frequent testing (every 3–6 months) for symptomatic patients and for high-risk patients:
	Multiple sexual partners
	STI clinic patients
	Adolescent clinics
	Correctional facilities
Human immunodeficiency virus (HIV)	Annual screening for all sexually active females <25 years
Treponema pallidum (syphilis)	Screening only recommended for pregnant females
	Testing recommended for symptomatic patients
Human papillomavirus (HPV)	Routine HPV screening not recommended
	Initial Papanicolaou (Pap) test recommended at age 21[a]
Other STIs:	Screening not recommended for asymptomatic patients
Hepatitis B	Testing recommended for symptomatic patients
Hepatitis C	
Herpes simplex virus	

Adapted from Workowski and Bolan (2015)
[a]Based on harmonized ACOG, American Cancer Society and US Preventive Services Task Force recommendations

maturation. Cervical maturation has been noted to progress more quickly in the presence of STIs secondary to inflammation, which also increases susceptibility to more infection (Moscicki et al. 2001). Conversely, hormonal contraceptive use and smoking have been noted to delay cervical maturation and prolong the presence of the cervical ectropion, again prolonging increased risk for STI transmission (Moscicki et al. 2001; Hwang et al. 2009).

18 Expedited Partner Therapy in Adolescents

The treatment of sexual partners of patients diagnosed with chlamydial or gonorrheal infections is known as expedited partner therapy (EPT) and is endorsed by CDC (Centers for Disease Control and Prevention 2015c).

The practice of EPT is quite important in the care of adolescents, as access to care can be difficult for this age group as discussed above. The use of EPT is also paramount for the prevention of the spread of infections, as well as decreasing rates of reinfection. The practice of EPT is permissible in the majority of the United States. The CDC provides up-to-date information on the legal status of EPT, including those states that prohibit the practice and those states in which it is permissible or potentially allowable. By June of 2015, EPT

remained prohibited in only four states: Florida, Kentucky, Ohio, and West Virginia (Centers for Disease Control and Prevention 2015c).

CDC has several recommendations for ways in which providers can provide services to partners and recommends treatment for male partners of female patients with gonorrheal or chlamydial infections (Centers for Disease Control and Prevention 2015c).

- Firstly, it is recommended that the patient receive treatment in the office as well as educational material, discussion of ways in which infections can be prevented in the future, and discussion of how to approach their sexual partner(s) so that they may also be treated. Providing the patient with information for her partner has been shown to increase rates of the partner seeking and receiving treatment for STI.
- If the patient is to return to the office for positive results and treatment, it is recommended that the provider contact the patient before the visit, notify her of the positive result(s), and encourage her to return for treatment with her partner; this facilitates evaluation and in-office treatment for the patient's sexual partner. This may be difficult for patients who have multiple sexual partners; CDC recommends providing educational material on STI and resources for STI testing and treatment to be issued to all partners in such cases. These methods can be employed for chlamydial, gonorrheal, syphilis, and HIV infection (Centers for Disease Control and Prevention 2015c).

With respect to chlamydial and gonorrheal infections, a method of EPT called patient-delivered partner therapy (PDPT) can be utilized for treating male partners of female patients (Centers for Disease Control and Prevention 2015c; Workowski and Bolan 2015).

- Providers can treat the patient in the office with the appropriate antibiotics: azithromycin 1 g orally once in the office for chlamydial infection.
- Ceftriaxone 250 mg intramuscularly once plus azithromycin 1 g orally once in the office for gonorrheal infection.

Where legal, the provider can then provide PDPT to the patient that she will then deliver to her sexual partner(s). The PDPT consists of medication that is packaged and labeled with instruction on use as well as treatment instructions, warning about medication use (for partners who are pregnant or have medication allergy), educational material on the STI, and material recommending that the partner seek care for any STI symptoms.

- The medications used for PDPT include azithromycin 1 g orally once for chlamydia treatment or cefixime 400 mg orally once and azithromycin 1 g orally once for gonorrhea treatment (Centers for Disease Control and Prevention 2015c; Workowski and Bolan 2015).

19 Cervical Cancer Screening in Adolescents

Infection with human papillomavirus (HPV) is quite common in sexually active young women. Despite this, the recommendations for cervical cancer screening with the Papanicolaou (Pap) test have changed in recent years (American College of Obstetricians and Gynecologists 2010; Snook et al. 2012).

Pap testing for cervical cytology in healthy young women is not recommended until age 21 years. In addition, routine HPV testing is not recommended when screening adolescents. This recommendation is based on the high rates of HPV infection in this age group and the high rates of spontaneous resolution; 90 % of HPV infection in this age group will resolve without treatment.

- Special considerations apply to patients with HIV infection, immunocompromised states (such as organ transplant) or on chronic immunosuppressants, as such patients require alternate screening schedules. Adolescents with HIV infection require two Pap test in the first year following infection (every 6 months) and annually thereafter if the previous Pap tests were normal.
- Immunocompromised adolescents should also have two Pap tests within the first year after first intercourse, then annually if the Pap tests were normal (American College of Obstetricians and Gynecologists 2010; Snook et al. 2012).

20 HPV Infection and Vaccination

Infection with HPV is the most common STI in sexually active patients (Centers for Disease Control and Prevention 2015b; Workowski and Bolan 2015). There are about 100 types of the HPV virus, 40 of which lead to genital infections. Most HPV infections are asymptomatic and are easily cleared by the body. A sexually active individual may become infected with HPV several times because of this (Workowski and Bolan 2015). Despite this, there are several high-risk strains of HPV that can lead to persistent genital infection. These strains are associated with anogenital warts as well as several types of malignancy, including oropharyngeal, penile, cervical, vaginal, and anal cancers. A vaccine was developed in an attempt to decrease the burden of disease associated with high-risk HPV infection (Centers for Disease Control and Prevention 2015b). There are now three HPV vaccines available that are given as a series of three shots over 6:

- Gardasil® 9, approved in 2014, protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.
- Gardasil® 4, approved in 2006, protects against HPV types 6, 11, 16, and 18.
- Cervarix®, approved in 2009, protects against HPV types 16 and 18. Cervarix® is only recommended for female patients.

By providing protection against infection with HPV types 16 and 18, the vaccines protect against infection with the strains that cause 66 % of cervical cancers. The addition of the five strains in Gardasil 9 adds protection against infection with strains associated with 15 % of cervical cancer. The vaccines that contain strains 6 and 11 provide protection against HPV strains that cause 90 % of anogenital warts, which can progress to cancers of the affected areas as listed above (Centers for Disease Control and Prevention 2015b; Workowski and Bolan 2015).

The HPV vaccines are generally well tolerated and are very effective at preventing HPV infection (Centers for Disease Control and Prevention 2015b). The vaccine series is generally recommended for patients between the ages of 9 and 26 years and is covered by most health insurance plans. There are few reported side effects with the HPV vaccine. These include pain at the injection site, fever, headache, fatigue, nausea, and muscle and joint pain (Centers for Disease Control and Prevention 2015b).

21 Special Consideration: Intimate Partner Violence and Sexual Assault

Most often, despite the fact that adolescence is a time when many individuals begin to show romantic interest in others and begin dating, little is discussed with them by providers about healthy relationships (Monasterio et al. 2010).

The provider can be an important role model for the adolescent who can discuss what a healthy relationship means. The Adolescent Health

Working Group recommends that providers relay simple messages about healthy relationships to adolescents by discussing some of the following:

- Two people who are partners in a relationship together are equals.
- Partners should be flexible with each other, especially regarding role behaviors.
- Partners should not assume an attitude of ownership toward the other.
- Partners should be encouraging toward each other and avoid manipulating or exploiting each other.

Often it is difficult for adolescents (and providers) to discuss such personal information on the initial office visit. These aspects of sexual history can and should be revisited at each office visit, especially as rapport improves. By discussing sexuality and healthy relationships openly, providers can help to prevent the adolescent from experiencing intimate partner violence, sexual assault, or sexual abuse (Monasterio et al. 2010; American College of Obstetricians and Gynecologists 2012b).

Intimate partner violence (IPV) affects both women and men from all age groups, socioeconomic groups, ethnicities, religion, sexual orientation, and levels of educational background (American College of Obstetricians and Gynecologists 2012b). The American College of Obstetricians and Gynecologists (ACOG) defines IPV as "a pattern of assaultive behavior and coercive behavior that may include physical injury, psychological abuse, sexual assault, progressive isolation, stalking, deprivation, intimidation, and reproductive coercion." These behaviors can be carried out by someone who is, was, or wishes to be in an intimate relationship with the victim. In addition, these behaviors occur as a means of exerting control over the victim. Adolescents are at high risk of IPV, as they are at a developmental stage where they seek relationships before they have a firm grasp of their personal identity. This trait makes them susceptible to manipulation by their partners. It is reported that one in ten high school females who are dating and one in five who are sexually active have experienced IPV in a given year; this includes IPV as defined above, as well as verbal and emotional abuse. Strikingly, these females are at increased risk of pregnancy, STI, substance use or abuse, and mental health issues, including suicidal ideation and attempt (Monasterio et al. 2010). Adolescents are manipulated by partners in many ways, including:

- Monitoring cell phone or social media use
- Digital dating abuse:
  - Posting sexual content (photos and/or videos) on social media against one's will
  - Stalking and/or humiliating through social and online networks
- Dictating what clothing is worn or even one's school attendance
- Manipulating contraception use (condoms as well as hormonal methods)

During adolescence, IPV perpetrators are equally likely to be male or female. In this age group, mutual aggression is common, and females are likely to be victims of physical abuse, while males are likely to be victims of psychological abuse (Monasterio et al. 2010). In addition, adolescents are commonly victims of IPV when their partners are older. Other factors that put adolescents at risk include substance abuse, low self-esteem, previous history of IPV, engaging in intercourse before age 15, having multiple partners, and pregnancy (Moscicki et al. 2001; American College of Obstetricians and Gynecologists 2012b).

Because IPV is so common, it is important for providers to routinely screen patients for IPV (American College of Obstetricians and Gynecologists 2012b). Once IPV is identified, providers should assess the safety of the patient and discuss involving the parents in the discussion and care. The provider can also use this encounter to educate the patient on IPV and ways to prevent it from recurring. If the adolescent is a minor, it is important for the provider to consider reporting the case as child abuse to child protective services. For adolescents over age 18, providers can report IPV in certain states, and providers should be

aware of local laws pertaining to IPV (Moscicki et al. 2001; American College of Obstetricians and Gynecologists 2012b).

Sexual abuse or sexual assault can occur as IPV or they can be independent of IPV (Moscicki et al. 2001; American College of Obstetricians and Gynecologists 2012b). Sexual abuse typically refers to the performance of a sexual act on a minor that is perpetrated by an adult. Though sexual abuse will not be discussed in this section, providers should be aware that they are mandated to report sexual abuse to child protective services. Sexual assault is any sexual contact that is nonconsensual and may include rape. Providers should be aware of local definitions as they vary by state (Kaufman 2008). Sexual assaults of adolescents are typically perpetrated by someone known to the adolescent, and victims commonly report substance use around the time of assault. It is estimated that 44 % of rape victims are minors and in these cases, reporting is mandatory.

For those over age 18, cases can be reported to local police; however some victims may not want to file a police report. Providers should be prepared to refer victims of sexual assault for a forensic exam within 72 hours to collect specimens if they are not equipped for and/or trained in such procedures; forensic exams are often performed at hospitals. Providers should provide EC to female victims as well as empiric treatment for chlamydial and gonorrheal infections and offer postexposure prophylaxis for possible HIV infection. The provider should also consider referral to mental health services, as posttraumatic stress disorder is common in victims of sexual assault (Moscicki et al. 2001; American College of Obstetricians and Gynecologists 2012b; Kaufman 2008).

22 Conclusion

Adolescence is a dynamic period of life with many physical and emotional variations. This makes the care of the adolescent or young adult patient intriguing and satisfying. The gynecologic care of adolescents includes conditions common to adult women, as well as conditions unique to the adolescent physiology. The adolescent is greatly affected by psychosocial factors, and this effect is more notable because of the adolescent's inherent inclination toward risk taking. Despite their independent nature, adolescents often look to providers as trusted adults to whom they can turn for advice and guidance, as well as for management of both common and unique medical conditions. Providers are encouraged to engage with their adolescent and young adult patients and to utilize the resources outlined in this chapter in their care.

23 Cross-References

- ▶ Abnormal Vaginal Bleeding During the Early Reproductive Years
- ▶ Anatomy of the Female Genital System
- ▶ Congenital Adrenal Hyperplasia in the Adolescent
- ▶ Congenital Anomalies of the Reproductive Tract
- ▶ Contraception and Family Planning
- ▶ Current Recommendations in Gynecology: Preventive Health Care, Screening, Immunizations
- ▶ Diagnosis and Management of Endometriosis
- ▶ Diagnosis and Management of Premenstrual Syndrome
- ▶ Gynecologic Care During the Early Reproductive Years
- ▶ Gynecologic History and Examination of the Patient
- ▶ Gynecological Care of the Adolescent
- ▶ Hyperandrogenism: Acne and Hirsutism
- ▶ Management of Acute Pelvic Pain: Torsion, Rupture of Ovarian Mass
- ▶ Management of Pelvic Pain, Dyspareunia, and Endometriosis
- ▶ Office Gynecology
- ▶ Preconception Care: In the Continuum of Women's Health Care
- ▶ Reproductive Endocrinology and Infertility

- ▶ Sexually Transmitted Diseases: Diagnosis and Work-Up (GC, Chlamydia, Herpes, HPV)
- ▶ Workup and Management of Polycystic Ovary Syndrome (PCOS)

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Congenital Adrenal Hyperplasia in the Adolescent

Mimi S. Kim, Teresa Tseng, Christina M. Koppin, and Mitchell E. Geffner

Abstract

Congenital adrenal hyperplasia (CAH) is a primary adrenal insufficiency and an autosomal recessive disorder that ranges in clinical severity from a classical, severe salt-wasting form to a mild, nonclassical form. In all patients, CAH involves adrenal hormone deficiencies and androgen excess. Females with CAH can have hyperandrogenism symptoms. Classical CAH presents in the newborn period with ambiguous genitalia in females and can be detected early in males with newborn screening. Clitoroplasty and vaginoplasty are surgical procedures that can correct ambiguous genitalia in females with CAH. Nonclassical CAH has a broader spectrum of clinical presentations, including premature pubarche, menstrual irregularities, and infertility. Glucocorticoid replacement therapy remains the mainstay of treatment, with the use of mineralocorticoid replacement in some classical patients and antiandrogen therapies in select female patients. Medication dosages, hormone levels, growth, and puberty need to be carefully monitored during childhood and adolescence, and hypercortisolism should be avoided in order to optimize final adult height and reduce potential morbidity. Long-term considerations of cardiovascular disease risk, bone mineral density, and fertility in adults remain under investigation.

Keywords

Congenital adrenal hyperplasia • Adrenal insufficiency • Cortisol deficiency • Cardiovascular risk • CAH • NCAH • Adolescent • Hyperandrogenism • 21-Hydroxylase deficiency • Childhood

Contents

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1 Introduction

1.1 Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that affects 1:10,000 to 1:20,000 children born worldwide (Speiser et al. 2010). CAH is a cause of primary adrenal insufficiency that results from a defect in the steroidogenic pathway, most commonly due to a mutation in the *CYP21A2* gene leading to 21-hydroxylase deficiency (21OHD) (Kim et al. 2012) present in ~95% of cases of CAH. The 11-hydroxylase deficiency (11OHD) is the next most common form present in ~5% of cases (Merke and Bornstein 2005; New et al. 2000; Kim and Donohoue 2014). Affected patients present with a spectrum of clinical severity and are classified as either severe (or classical) or late onset (or nonclassical; NCAH), depending on their specific mutations of the *CYP21A2* gene. There are 12 common mutations of the *CYP21A2* gene that can be commercially tested for as part of a screening multiplex panel, including small and large gene deletions and amino acid substitutions (Charmandari et al. 2002a). Rarer CYP21A2 mutations can be assessed by gene sequencing. This chapter will focus on patients with CAH due to 21OHD. Unless otherwise stated, CAH refers to the 21OHD form hereafter.

1.2 Classical Congenital Adrenal Hyperplasia

Patients with classical CAH have several complete or near-complete hormone deficiencies including cortisol, aldosterone, and epinephrine (Merke and Bornstein 2005; Kim et al. 2014). Affected patients also have androgen excess driven by increased ACTH levels that result from cortisol deficiency. Among patients with classical CAH, the salt-wasting (SW) form occurs in ~67% of patients and the simple-virilizing (SV) form in ~33% of patients (Merke and Bornstein 2005). Newborns and children with SW CAH suffer from near-complete aldosterone deficiency, which can result in significant salt loss from the kidneys. If left untreated, affected patients can develop salt-wasting crises which can lead to death. Patients with SV CAH maintain ~1–2% of enzyme activity and are at risk for adrenal crisis to a lesser extent than those with SW CAH (New et al. 2013). Females with either form of classical 21OHD (as well as those with 11OHD) are typically identified at birth secondary to ambiguous genitalia; however, males can take much longer to diagnose because of lack of genital ambiguity (Merke and Bornstein 2005).

To this point, newborn screening for classical CAH has altered clinical practice permitting the early identification of both male and female newborns with classical CAH (generally in the first week of life). In the USA, screening for classical CAH due to 21OHD was instituted on a state-by-state basis beginning with Alaska in 1977 (Pang et al. 1982) and in all states, Washington DC, and Guam by 2008 (Kim and Donohoue 2014).

Classical CAH is more common in certain ethnicities (most frequently in Alaskan Aleutian Yupik Eskimos) and does not commonly affect African American, Asian, and East Indian populations (Merke and Bornstein 2005; New et al. 2013). The results of ACTH stimulation testing (cosyntropin 250 mcg IV) can be used to help differentiate between classical CAH subtypes depending on the 60′ stimulated 17-OHP level. In general, SV CAH patients have stimulated 17-OHP levels of 10,000–25,000 ng/dL, whereas SW CAH patients have stimulated 17-OHP levels up to 100,000 ng/dL.

1.3 Nonclassical Congenital Adrenal Hyperplasia

21OHD is also the most common cause of NCAH, the mildest form of CAH, with an overall prevalence of 1:1000 (Finkielstain et al. 2012). Higher rates for NCAH are seen in certain ethnic groups,

including Ashkenazi Jewish (1:27), Hispanic (1:40), Yugoslav (1:50), and Italian American (1:300) populations (New 2006).

Patients with NCAH due to 21OHD maintain 20–50% of normal 21-hydroxylase activity, resulting in a milder phenotype than seen in patients with classical CAH (Witchel and Azziz 2010).

However, as a result, signs and symptoms of virilization can vary and be difficult to predict (Kashimada et al. 2008). Signs and symptoms seen in affected patients are secondary to androgen excess and can include premature pubarche, growth acceleration, and advanced bone age in growing children, along with hirsutism, acne, delayed menarche, menstrual irregularities, and infertility in adolescent and adult females (Pall et al. 2010). Symptoms typically present during adolescence, although most patients with NCAH due to 21OHD are thought to be asymptomatic and may never be diagnosed (Witchel 2013).

- If symptomatic, the clinical phenotype in females is similar to that seen in patients with polycystic ovarian syndrome (PCOS), another androgen excess disorder (Rosenfield et al. 2015). PCOS is the most common symptomatic androgen excess disorder, affecting 6–10% of reproductive-age women (Pall et al. 2010; Rosenfield et al. 2015).
- Less common effects of excess androgens that potentially may occur in patients with either NCAH due to 21OHD or PCOS include an enlarged clitoris and ovarian cysts (Kim and Donohoue 2014). NCAH due to 21OHD has been identified in 2–3% of women with hyperandrogenism (Escobar-Morreale et al. 2008; Fanta et al. 2008).

Unstimulated early morning serum 17-OHP levels in females with NCAH due to 21OHD are generally mildly elevated between 170 and 300 ng/dL (Kim and Donohoue 2014). However, patients with NCAH due to 21OHD may also have normal unstimulated 17-OHP levels, and conversely, women with PCOS may have mildly elevated 17-OHP levels (Pall et al. 2010).

- Therefore, to differentiate between these entities, ACTH stimulation testing should be employed. In patients with NCAH due to 21OHD, 60-min 17-OHP levels are generally between ~1200 and 10,000 ng/dL. Although the minimal stimulated "cutoff" level of 17-OHP has been debated, it is still much higher than the ACTH-stimulated 17-OHP level in patients with PCOS (Merke and Bornstein 2005; Kim and Donohoue 2014; Pall et al. 2010).

In addition, women with classical CAH may develop secondary PCOS (Rosenfield et al. 1994), with an increased incidence of polycystic ovaries found on ultrasound in women with CAH (Kim and Merke 2009).

2 Puberty/Adolescence

Postnatal exposure to androgen excess occurs in patients with CAH under suboptimal hormonal control. It is, therefore, vital to closely monitor the hormonal levels of patients with all forms of 21OHD to ensure proper growth and puberty.

Optimizing hormonal control can also aid in avoiding morbidity associated with the development of irregular menses, obesity, hypertension, osteoporosis, and adrenal rest tumors (Finkielstain et al. 2012). This can be particularly important during adolescence, when sex hormones, rapid growth, and transition to independence can make it challenging for teenagers to achieve good hormonal control, either because of nonadherence or unpredictable physiology. When females with classical CAH are adequately treated, many have regular menses following menarche (Premawardhana et al. 1997), although, if poorly controlled, they may have primary amenorrhea or delayed menarche (Richards et al. 1978).

Short final adult height can result from hypercortisolism and/or hyperandrogenism, with a large study in the USA noting an average loss in final adult height of -1.0 ± 1.1 SD in adults with classical CAH (-15.0 ± 16.5 cm for males and

-10.8 ± 11.9 cm for females) and -0.4 ± 0.9 SD in adults with NCAH (-6.0 ± 13.5 cm for males and -4.3 ± 9.7 cm for females) (Finkielstain et al. 2012). Another pediatric study showed similar results, with final adult height ~10 cm below the midparental height (Lin-Su et al. 2011), and a large adult study in the UK noted an average height loss in males with classical CAH of 10.4 cm and 6.4 cm in women (Han et al. 2014). Secondary to androgen excess, children with classical CAH can develop premature pubarche/adrenarche, manifested by early-onset pubic and/or axillary hair, acne, undue bone age advancement, and accelerated growth, with secondary central precocious puberty (breast development $<$ 8 years in girls and testicular development $<$ 9 years in boys) in some severe cases. Thus, all children with classical CAH need to be monitored clinically for signs of early puberty, an unexpected increase in growth rate, and bone age advancement on x-ray, as these complications can negatively impact final adult height. Youth with NCAH can also develop these complications and should be monitored for abnormal growth and puberty (Witchel 2013).

3 Medical Management

3.1 Daily Medication Management

The clinical management of CAH focuses on two main goals: replacement of hormone deficiencies and suppression of androgen excess. The mainstay of treatment in children is glucocorticoid (GC) replacement with hydrocortisone. For patients with the salt-wasting form of CAH, and some patients with simple-virilizing form, daily fludrocortisone replacement is necessary to correct real or subclinical mineralocorticoid (aldosterone) deficiency. Physiological studies have shown that the secretion rates of aldosterone remain constant throughout life in normal individuals (Weldon et al. 1967). In patients with CAH, the recommended dosing of fludrocortisone is also relatively constant at 0.05–0.2 mg/day, divided into once- or twice-daily doses (Speiser et al. 2010). From infancy until approximately 1 year of age, sodium chloride supplementation of 1–2 gm/day or 4 mEq/kg/day divided into four daily doses and given along with feedings is also recommended, as breast milk and formula contain inadequate amounts of sodium to protect against salt wasting in infants with CAH secondary to 21OHD (Mullis et al. 1990). Routine laboratory testing of electrolyte levels and plasma renin activity can help guide fludrocortisone and sodium chloride dosing.

To assess the efficacy of GC replacement, measurement of serum steroids should always be undertaken at the same time of day and with the same duration of the time from the last dose of medication (e.g., immediately before the morning hydrocortisone dose at 7 AM, 8 h after the bedtime dose of hydrocortisone at 11 PM). This standardization of testing conditions is critical to allow comparisons to previous laboratory values for accurate monitoring (Merke and Bornstein 2005; Merke and Poppas 2013). Care must be taken to avoid overtreatment with GC, in an attempt to suppress excess androgen levels, as this could lead to deleterious effects on multiple organ systems. The balancing act between controlling hyperandrogenism and avoiding hypercortisolism remains a challenge for clinicians and demands regular follow-up care. Routine laboratory monitoring of serum steroids, typically including 17-OHP, androstenedione, and/or testosterone, every 3–6 months is used to assess efficacy of GC dosing (Speiser et al. 2010).

Appropriate dosing is also critical to avoid the risk of adrenal crisis and accelerated growth plate maturation and closure from adrenal androgen excess as a result of undertreatment while also avoiding the consequences of iatrogenic Cushing syndrome with overtreatment.

Radiography of the left wrist for bone age evaluation should be done semiannually or annually, after the age of 2 years, to detect undue advancement in bone age compared to chronological age, which, if present, would be a marker of chronic poor disease control (Speiser et al. 2010).

For the growing child with CAH, hydrocortisone tablets are the most appropriate GC

medication to replace deficient cortisol and to thereby suppress ACTH and adrenal androgen production.

- Hydrocortisone dosing of 10–15 mg/m^2/day is typically divided into three daily doses, although more frequent dosing might be necessary in some patients to achieve hormonal control. A large dose in the evening/bedtime is used in patients with CAH to suppress the early-morning surge of ACTH and subsequent peak androgen overproduction by morning (Merke and Poppas 2013), with the next highest dose given in the morning, in concordance with the AM cortisol surge. In adults, a larger hydrocortisone dose at bedtime may not be feasible secondary to sleep problems, so an alternative is to give the highest dose in the morning, mimicking the diurnal pattern of cortisol production; in children, either dosing pattern did not differ in sleep activity or disease control (German et al. 2008).
- For postpubertal adolescent patients who have nearly or completely finished their linear growth, a longer-acting GC can be used for more convenient once- or twice-daily dosing. Liquid formulations, such as prednisolone suspension or dexamethasone elixir, also allow for greater fine-tuning of the daily dose. Recommended dosing, in terms of hydrocortisone equivalents, remains 10–15 mg/m^2/day (Speiser et al. 2010).

The relative potency of long-acting GC medications varies among subjects depending on pharmacokinetic metabolism. Therefore, similar to hydrocortisone, dose titration should be based on laboratory monitoring and symptoms (Speiser et al. 2010), with the goal of providing the smallest GC dose in order to effectively replace the GC deficiency and suppress adrenal androgens and thereby avoid associated comorbidities, such as short final adult height. During adolescence, potentially adverse effects of GCs on final adult height can be reduced if the hydrocortisone equivalent dosing is less than 17 mg/m^2/day (Bonfig et al. 2009).

3.2 Sick Day Management

The normal physiological response to acute illness or trauma involves a coordinated neuroendocrine mechanism, including increases in stress hormones: epinephrine, cortisol, and growth hormone. The rise in counter-regulatory hormone levels protects against hypoglycemia via gluconeogenesis and glycogenolysis (Kim et al. 2014).

In patients with CAH, additional GC medication, often referred to as a "stress dose," must be given promptly to mimic the physiological cortisol stress response and avoid adrenal crisis during acute illness or trauma. Situations requiring a stress dose include fever $\geq$ 100.4°F, vomiting, diarrhea, and physical trauma (i.e., broken bone or concussion).

- The daily oral maintenance dose of GC is increased for moderate or severe illness, with ~25–30 mg/m2/day of hydrocortisone or its equivalent for moderate illness and 50 mg/m2/day (divided into Q6 hour dosing) during times of severe illness.
- If there is vomiting shortly after an oral stress dose, the oral stress dose should be repeated.
- Small frequent sips of clear fluids containing glucose are recommended for illnesses with vomiting and/or diarrhea. In situations where oral stress dosing is not possible (i.e., repetitive vomiting within 30 min, loss of consciousness, seizures, etc.), hydrocortisone should be administered via an intramuscular (IM) injection without delay.

Caregivers should be trained to recognize situations when IM hydrocortisone is indicated and be able to administer this injection to their child (or to themselves beginning in young adulthood). An emergency hydrocortisone injection kit with medication, sterile saline solution, and injection supplies (hypodermic needle, alcohol wipes, and band aids) should be easily accessible or carried with the patient at all times for emergency use. Combination medication storage devices, such as the Act-O-Vial® kit, allow for the rapid mixing of hydrocortisone powder with sterile injection

solution and reduce dilution steps required to administer the injection.

- Simple age-based dosing guidelines for IM hydrocortisone are 25 mg for infants and toddlers, 50 mg for children, and 100 mg for adolescents/adults (Speiser et al. 2010).

A medical identification bracelet/necklace and/or wallet card stating that the patient has "adrenal insufficiency and needs hydrocortisone," along with an emergency letter, is recommended for reference by first responders and/or paramedics in case of a medical emergency such as a motor vehicle accident. The rapid identification of patients with adrenal insufficiency would enable the administration in the field of an emergency stress dose of hydrocortisone in order to mimic the physiological stress response to illness or trauma. Injection of hydrocortisone should be given in a timely fashion and not be delayed until presentation at the emergency department.

3.3 Other Medications

To counteract adverse effects of hyperandrogenism, such as hirsutism, in adolescent and adult females, adjunctive therapies can be considered, including oral contraceptive pills (OCPs) and spironolactone. OCPs suppress ovarian androgen production and increase the level of sex hormone-binding globulin (SHBG), which also reduces the serum concentration of free testosterone (Merke and Poppas 2013).

OCPs containing antiandrogens such as drospirenone or cyproterone (not available in the USA) may prove to be more effective in combating manifestations of hyperandrogenism in these young women (Matthews and Cheetham 2013). Spironolactone has antiandrogenic effects that can aid in the reduction of hirsutism and acne. However, its use may require an increase in the mineralocorticoid replacement medication, fludrocortisone, in classical CAH patients (Auchus and Arlt 2013).

Another nonsteroidal antiandrogen medication, flutamide, has been used to treat patients with PCOS and has been used in an off-label manner in patients with classical CAH (Auchus and Arlt 2013). Flutamide has been studied experimentally in combination with an aromatase inhibitor in children with CAH, helping to maintain normal growth velocity and bone maturation (Merke et al. 2000; Hero et al. 2005).

Although not standard of care, gonadotropin-releasing hormone (GnRH) analog therapy (i.e., leuprolide or histrelin) has been utilized clinically for children with CAH who exhibit central precocious puberty to temporarily halt pubertal progression and thereby preserve final adult height. Otherwise, short final adult height can result from early growth plate closure resulting from either poor hormonal control and/or overtreatment with GC (Han et al. 2014). In some cases, growth hormone injections have been used off-label to increase height velocity in combination with a GnRH analog to slow central puberty and growth plate closure associated with advanced bone age (Quintos et al. 2001).

3.4 Multidisciplinary Team Approach and Transition to Adult Care

Coordination of care and communication between primary care provider and subspecialty team members, including endocrinologist, urologist, and gynecologist, is crucial to ensure optimal treatment of the patient with CAH. The multidisciplinary team approach includes collaboration with psychosocial services to address potential psychological distress in both the patient and parents (Auchus et al. 2010). Routine assessment of quality of life by providers is encouraged to determine the impact of medical management and surgical interventions pertaining to CAH-related care (Speiser et al. 2010).

The transition to adult care should be initiated by conversations with parents and patient during early adolescence and progress throughout the teenage years to include a written plan that increases self-care responsibilities for the patient and identifies adult providers in a new medical home (Cooley and Sagerman 2011).

Ideally, specialty clinics jointly staffed by pediatric, reproductive, and adult endocrinologists, along with gynecologists and urologists, can ease the transition to adult care and conveniently allow for multiple providers to see the patient at the same clinical encounter. Specifically, adolescent girls with CAH with virilization require consultation with a gynecologist prior to and/or during early puberty. An examination under anesthesia is recommended, and joint examination with an experienced pediatric urologist is also recommended (Speiser et al. 2010). Discussion with the patient and family about potential issues related to sexual activity should be discussed with the patient and family regarding the possible need for surgical intervention. This topic will be discussed further in the section on "Surgical Considerations."

3.5 Fertility and CAH

Fertility rates in CAH women have been reported as reduced despite normal pregnancy rates (Casteras et al. 2009). However, lower pregnancy rates have also been found in CAH women compared to controls (Helleday et al. 1993) with elevated progesterone postulated as a potential etiology. The pregnancy rates may remain low despite the addition of fertility treatments (Hagenfeldt et al. 2008). In women with NCAH who are untreated, the fertility rate has been reported to be 50% (Feldman et al. 1992). CAH males who develop testicular adrenal rest tumors (TART) may experience testicular damage leading to infertility in adulthood (Claahsen-van der Grinten et al. 2009). This topic will be further discussed in the following section on "Comorbidities."

4 Comorbidities in CAH

4.1 Bone Mineral Density

Lifelong GC therapy in patients with CAH has the dual goals of physiological hormone replacement and suppression of excess adrenal androgens. However, if not titrated properly, long-term therapy could lead to concerns for secondary osteopenia and osteoporosis in adulthood.

Mechanistically, GCs both suppress osteoblast activity and promote osteoclast activity, lead to early epiphyseal closure, and blunt the GH-IGF-I axis (Hofbauer et al. 1999; Falhammar et al. 2007). Studies are inconsistent in showing lower bone mineral density in patients with CAH compared to controls, and the risk of osteoporosis-related fractures in CAH seems to be equivocal in premenopausal women (Falhammar et al. 2007; Sciannamblo et al. 2006; Koetz et al. 2012). It has been hypothesized that the ill effects of chronic, supraphysiological GC therapy are counteracted by elevated androgen levels in patients with CAH. These androgens in turn are converted to estrogens, which are known to inhibit osteoclast bone resorption (Lin-Su and New 2007). Thus, the goal of daily GC medication dosing should focus on using the minimum effective GC dose to appropriately lower 17-OHP and androgen levels as high total cumulative and average daily GC doses have been associated with decreased bone mineral density in patients with CAH (Chakhtoura et al. 2008).

Individuals with CAH have been found to have rates of vitamin D deficiency and insufficiency consistent with those in the general population (Finkielstain et al. 2012; Looker et al. 2011). With this in mind, regular physical activity and calcium and vitamin D supplementation are recommended for osteoporosis prevention beginning in adolescence.

4.2 Adrenal Rest Tumors

Poor control of CAH, especially cases requiring adrenalectomy, can lead to the development of adrenal rest tumors in gonadal tissue due to hypersecretion of ACTH and the expression of ACTH-specific receptors on the adrenal tissue in the testes (TARTs) or ovaries (OARTs) (King et al. 2009). TARTs have been observed more frequently in the testicles of male patients with poorly controlled CAH (Claahsen-van der Grinten et al. 2009). More recently, case studies have reported on the presence of OART in female

CAH patients with poor disease control (Tiosano et al. 2010; Thomas et al. 2013). The prevalence of OART is rare with less than two dozen case reports in the literature, which is far less common than the male counterpart phenomenon of TART that has been observed to occur in up to 95% of male CAH patients, especially with increasing age and/or poor CAH control (Finkielstain et al. 2012; Zaarour et al. 2014; Mouritsen et al. 2010; Arlt et al. 2010). Of note, more advanced imaging techniques such as PET/CT scans have been shown to visualize OART tissue when the first-line ultrasound modality does not detect abnormalities (Crocker et al. 2012). Regardless, adrenal rest tumors in either the testis or ovary can potentially interfere with the reproductive function of these organs, including menstrual cycles, and, in the worst case, lead to secondary infertility (Claahsen-van der Grinten et al. 2009; Thomas et al. 2013).

In terms of screening, it is recommended for males to be screened for TARTs starting no later than adolescence (Speiser et al. 2010) although recommendations vary depending on the group and include screening children (Finkielstain et al. 2012; Claahsen-van der Grinten et al. 2009). It is recommended that transabdominal and pelvic ultrasounds be conducted to evaluate the ovaries for cysts and adrenal rest tumors in females with CAH where ovarian dysfunction is suspected (Zaarour et al. 2014).

4.3 Cardiovascular Disease Risk Factors

Increased cardiovascular disease (CVD) risk factors are commonly seen in adults (Falhammar et al. 2015) and children (Finkielstain et al. 2012; Falhammar et al. 2015; Subbarayan et al. 2014) with classical CAH secondary to 21OHD, including abnormal cholesterol fractions, insulin resistance, obesity, and hypertension. Across various studies, there are mixed reports of associations with glucocorticoid and mineralocorticoid replacement therapies.

Childhood obesity rates in CAH exceed the high/epidemic rates seen in unaffected normal children in the USA and several other developed countries (Finkielstain et al. 2012; Subbarayan et al. 2014; Volkl et al. 2006; Cornean et al. 1998). Obesity is an important cardiovascular disease risk factor, making it a concerning complication facing youth and adults with CAH. The etiology for obesity in CAH is not entirely clear; hyperandrogenism, lifelong glucocorticoid treatment, and hormonal imbalances inherent in classical CAH are potential contributing factors (Finkielstain et al. 2012; Kim and Merke 2009; Arlt et al. 2010). Abnormally elevated leptin levels in CAH individuals could also be an important factor, as otherwise healthy obese individuals also exhibit elevated leptin (Charmandari et al. 2002b).

Increases in fat mass measured by different techniques such as simple skinfold thickness, bioelectrical impedance analysis, and whole-body dual-energy x-ray absorptiometry are concerning (Cornean et al. 1998; Isguven et al. 2008; Stikkelbroeck et al. 2003). As well, abdominal adiposity has been shown to be increased in adolescents and young adults with classical CAH due to 21-hydroxylase deficiency, using single-slice computed tomography (Kim et al. 2015). Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are both increased in CAH, with a higher proportion of pro-inflammatory VAT than SAT, than was seen in matched controls. VAT in particular is strongly associated with metabolic syndrome and cardiovascular disease, and this unfavorable abdominal fat distribution (for the same degree of obesity) is particularly concerning. In adolescents and young adults with CAH, VAT and SAT strongly correlated with measures of obesity such as the waist-to-height ratio and fat mass. As well, there were strong correlations between abdominal adiposity and inflammatory markers [plasma activator inhibitor-1 antigen (PAI-1), highly sensitive C-reactive protein (hs-CRP), and leptin], low-density lipoprotein cholesterol (LDL), and homeostasis model assessment-estimated insulin resistance index (HOMA-IR). Interestingly, no sex differences were noted for either VAT or SAT in individuals with CAH.

There is evidence for insulin resistance in children and adolescents with classical CAH (Finkielstain et al. 2012, Charmandari et al. 2002b;

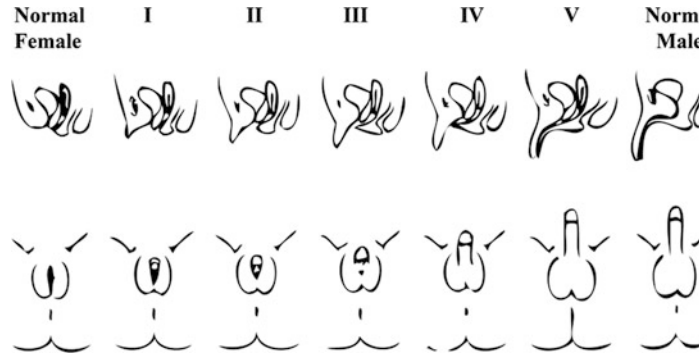

Fig. 1 Prader scale for ambiguous genitalia in females (Adapted from Prader and Gurtner 1955)

Sartorato et al. 2007; Williams et al. 2010) using either HOMA-IR or oral glucose tolerance testing. Hyperandrogenism itself may contribute to hyperinsulinism, as studied in adolescent and adult females without CAH (Kim and Merke 2009), which could potentially translate to the hyperandrogenic cohort of females with CAH. The epinephrine deficiency seen in patients with classical CAH, secondary to impaired adrenomedullary development, has been associated with elevated insulin and leptin levels and may contribute to insulin resistance (Kim and Merke 2009; Charmandari et al. 2002b).

High blood pressure is commonly seen in children. Potential etiologies that have been studied include changes in mineralocorticoid sensitivity in infants contributing to transient hypertension, excessive GC and/or fludrocortisone dosages, and obesity. Fludrocortisone dosages are relatively larger for body size at younger ages, although the dose does not tend to correlate with blood pressure. Overall, elevated BMI or obesity has not been associated with hypertension in CAH children (Finkielstain et al. 2012; Bonfig and Schwarz 2014; Nebesio and Eugster 2006). Hypertension, or higher blood pressure compared to controls, has recently become more commonly observed in adults with classical CAH (Finkielstain et al. 2012; Arlt et al. 2010; Subbarayan et al. 2014; Mooij et al. 2011).

Carotid intima media thickness (CIMT), a marker of subclinical atherosclerosis, has been found to be greater in young adult with CAH than in matched controls (Sartorato et al. 2007). These differences are not observed in children and adolescents with CAH (Harrington et al. 2012; Amr et al. 2014; Kim et al. 2016). However, a study looking at subgroups of CAH adolescents with poorly controlled disease found correlations between chronic hyperandrogenism and increased CIMT (Kim et al. 2016). These findings are consistent with the detection of increased CIMT in women with PCOS compared to controls (Meyer et al. 2012) and the increased CIMT seen in adult males compared to adult females. Adult women without CAH have later CVD manifestations than adult men, beginning in middle-to-late adulthood (Mendis et al. 2011). Maintaining good hormonal control is, therefore, potentially important in preventing the development of this CVD risk factor in patients with CAH, a population already predisposed to obesity, hypertension, and insulin resistance.

5 Surgical Considerations

The mutation in 21-hydroxylase results in excess androgen exposure beginning in utero during critical developmental periods and results in variable degrees of virilization of the external genitalia of newborn girls, including characteristics of clitoromegaly, fused labia majora, and a common urogenital sinus (Kim and Donohoue 2014). The Prader scale is used to describe the degree of virilization (Fig. 1).

The presentation of ambiguous genitalia at birth should raise suspicion for the diagnosis of a female with CAH secondary to 21OHD, in particular if there is a male-appearing child with bilateral cryptorchidism.

Although the external genitalia can be partially or even fully male appearing (without palpable

testes) in patients with CAH, the internal female reproductive structures (ovaries, fallopian tubes, uterus, and proximal vagina) in girls are unaffected and have the potential to function normally in regard to menstruation and pregnancy later in life.

Of note, the external genitalia of newborn male infants with CAH are normal, notwithstanding the presence of hyperpigmentation, and are not adversely affected by the excess androgen exposure in utero. Historically, this often resulted in a delayed diagnosis of CAH, with the male patient presenting with early adrenal crisis or later with precocious pubarche, rapid growth, and advanced bone age. With the implementation of newborn screening for CAH, this presentation should rarely if ever occur.

Surgical considerations for females with CAH have been a debated topic in regard to the extent of procedures to be performed and the age at which to perform them. Regardless of these debates, prior to any consideration of surgery, it is critical that the patient is medically stable; that the caregivers are fully informed and understand the indications, risks, benefits, and alternatives to the procedures; and that an experienced pediatric urologist (or pediatric surgeon with significant experience in these specific procedures) performs the planned surgery (Auchus et al. 2010). Also critical is the support of experienced pediatric endocrinologists, anesthesiologists, and social workers.

Androgen exposure causes enlargement/elongation of the clitoris, regression of distal vaginal/introital structures, fusion of the labia majora, and progressive tubularization of the urethra/common genitourinary sinus tissue.

In the past, CAH females with virilization would often undergo a feminizing genitoplasty procedure early in life. In fact, the American Academy of Pediatrics still generally recommends that genital surgery be performed in the first 15–18 months of life, prior to development of genital awareness (Hughes et al. 2006). Depending on the degree of virilization and level of the vaginal confluence, reconstructive procedures may include vaginoplasty, labioplasty, and/or clitoroplasty. However, some believe that vaginoplasty during infancy carries higher risks of vaginal stenosis requiring dilation or surgical revision later in life (Speiser et al. 2010). There is no precise objective criterion for when a clitoroplasty should be performed. Should a clitoroplasty be done, care must be taken during the dissection to preserve the clitoral head and neurovascular bundles to maintain sensation (Lee and Witchel 2002). Benefits of early vaginoplasty may include a reduction in the risk of urinary tract infections (primarily in those with a significant common urogenital sinus); shorter surgical distances; elastic tissues; improved wound healing, creating a functional vaginal opening to allow for menstrual flow; and early attainment of normal-appearing external genitalia prior to genital awareness. It may promote normal patient psychosexual development and social acceptance, as well as alleviate parental distress (Speiser et al. 2010). Procedures performed during infancy (prior to 12 months of age) benefit from the presence of more elastic vaginal tissue related to elevated estrogen levels. These estrogen levels are a result of the "mini-puberty of infancy," a physiological activation of the hypothalamic-pituitary-gonadal axis that begins in the first month of life and wanes to prepubescent levels over the first 2 years for females (Kuiri-Hanninen et al. 2014).

The most current consensus statement for the care of patients with virilizing CAH recommends vaginoplasty be performed using a urogenital mobilization approach prior to 12 months of age for patients with significant virilization (Prader score $\geq$3) (Speiser et al. 2010).

Vaginoplasty can in some cases be performed before age 6 months by an experienced pediatric urologist when the child is suffering from recurrent urinary tract infections (Auchus et al. 2010). A partial urogenital mobilization (PUM) or limited proximal dissection is generally preferred over a total urogenital mobilization (TUM) procedure, which involves proximal dissection deep to the urogenital diaphragm, because of concerns about disruption of important urethral muscular and support structures involved in urinary continence.

The PUM or limited proximal dissection procedure was described in detail by Rink et al. (2006) and has been reported to produce cosmetic and urinary functional outcomes in most cases of

females with virilization from CAH while potentially reducing morbidity in comparison to the more extensive TUM procedure. The PUM procedure has reported advantages of an increased likelihood of preserving clitoral innervation, avoidance of dissection of supportive tissues around the bladder neck, and reduction of vaginal foreshortening compared to the TUM procedure (Rink et al. 2006). In some cases, however, the PUM procedure may need to be converted to a TUM procedure if the vagina remains a significant distance from the perineum after PUM.

Caregivers may decide to delay vaginoplasty for the female CAH patient who does not have significant virilization (i.e., Prader score <3). The potential benefits of delaying surgery until the patient has reached puberty may include a reduced risk of developing vaginal stenosis and the associated need for dilation therapy or surgical revision (Speiser et al. 2010). Choosing to delay surgery until puberty also allows the patient to take part in the decision-making and has the advantage of more elastic vaginal tissue associated with elevated estrogen levels during adolescent puberty. Conversely, delayed reconstructive surgery results in greater distances from the perineum to the vagina and carries higher risks of wound infection/wound-healing issues due to local colonization of mature hair follicles. Emotional distress can also be a significant issue for surgical patients when extensive external anatomical changes and gender role changes are required (Woelfle et al. 2002). The typical technique used is the Fortunoff posterior flap vaginoplasty, which is indicated if the entry point of the vagina into the common urogenital sinus is low, as is often the case with Prader score of <3 (Schaeffer et al. 2010). Long-term studies with standardized outcome measures are needed to investigate whether early vaginoplasty during infancy or a delayed vaginoplasty during adolescence leads to more favorable outcomes regarding urinary continence, rate of urinary tract infections, sexual and reproductive function, and psychological outcomes.

If indicated, clitoroplasty should be performed concurrently with vaginoplasty during infancy or adolescence. Reduction clitoroplasty has been the most commonly performed procedure for clitoromegaly associated with CAH (Poppas et al. 2007). A dorsal nerve-sparing technique for the reduction clitoroplasty procedure to preserve innervation of the glans clitoris and future sexual function has been described, involving excision of corpora cavernosa tissue at a starting point that is 1.5–2 cm distal to the bifurcation allowing for elevation and support of the glans clitoris and preserving clitoral erection during arousal (Poppas et al. 2007). Initial studies on clitoral viability and sensitivity outcomes after clitoroplasty show preservation of vascular blood flow and sensitivity following the dorsal nerve-sparing clitoroplasty (Yang et al. 2007). However, long-term follow-up on sexual function outcomes are still lacking.

Some may consider the clitoroplasty procedure as a cosmetic procedure and not medically necessary, as it does not reduce morbidity in the same way that vaginoplasty can allow for normal menstrual flow and sexual function, and reduce the risk for frequent urinary tract infections. However, others strongly argue that the procedure is necessary for the appropriate psychosocial development of the child and to avoid significant distress caused by having different-appearing genitalia (Speiser et al. 2010). Therefore, caregivers must be fully informed and demonstrate understanding of the indications, benefits, risks, and alternatives for the procedure prior to electing to have their child undergo a clitoroplasty. Whether caregivers choose to pursue a clitoroplasty for their child at the time of vaginoplasty, or elect not to have the clitoroplasty done, providers should be supportive of the decision and provide follow-up consultation as needed.

6 Conclusion

There is a wide spectrum of clinical phenotypes in CAH and morbidity related to both hormone deficiencies and androgen excess inherent to the condition. Adolescents with CAH need to be monitored carefully for proper growth and pubertal development to optimize final adult height and avoid other comorbidities.

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7 Cross-References

- Congenital Anomalies of the Reproductive Tract
- Hyperandrogenism: Acne and Hirsutism
- Treatment of Gynecological Congenital Anomalies
- Workup and Management of Polycystic Ovary Syndrome

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Benign Vulvar and Vaginal Pathology

Daman Samrao

Contents

Abstract

Benign vulvar and vaginal pathology is common, consisting of a wide variety of lesions which include inflammatory conditions, pigmented lesions, neoplastic and nonneoplastic masses, and cysts. Women of all ages are affected. The majority of these lesions are clinically insignificant unless symptomatic or when they mimic malignancy. Rare lesions with premalignant potential are also present.

Keywords

Lichen sclerosus • Papillary hidradenoma • Vulvar melanosis • Atypical melanocytic nevi of genital type • Fibroepithelial polyp • Dysplastic nevi • Bartholin's gland cyst • Mullerian cyst • Epithelial inclusion cyst

1 Introduction

The high prevalence of benign lesions of the vulva and vagina makes the clinical and pathologic recognition of these entities important. Some of these lesions can lead to significant morbidity, and some are even considered premalignant. Successful treatments are available for most all these lesions. We discuss the most common and clinically relevant of these in this chapter.

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2 Lichen Sclerosus

2.1 Introduction

Lichen sclerosus (LS) is a chronic, progressive, and debilitating dermatosis which remains poorly understood despite its recognition in the late nineteenth century. The hallmark of the disease is progressive scarring of the skin manifested grossly as white plaques and epidermal atrophy and histologically as dermal sclerosis with chronic inflammation. It affects males and females, adults and children, and all races but has a predilection for postmenopausal Caucasian women. It can involve any part of the skin but predominantly affects the anogenital region with only 6 % of cases presenting as pure extragenital lesions. Of the vulvar dermatoses, it is the most common accounting for 39 % of all cases. The prevalence of LS is estimated to be 0.1–1.7 % but is likely an underestimate due to patient's presenting to numerous clinical settings, lack of clinical diagnosis, and underreporting by patients due to lack of symptoms or embarrassment.

The etiology of LS remains unknown and controversial. Interplay between immunologic alterations and chronic inflammation is believed to result in the formation of sclerosis. The development of LS in patients after surgery, trauma, instrumentation, and genital piercings supports this theory. Autoimmune and genetic components are strongly favored to play a part. Autoantibodies against extracellular matrix 1 (ECM1) protein and the basement membrane zone (BMZ) [BP180 and BP230] have been described in. *Borrelia burgdorferi* and Epstein Barr virus have been implicated as causative agents, but no strong evidence exists to support their involvement. Other possible causes include hormonal influences due to the presence of decreased dihydrotestosterone in affected females and the presentation of the disease at times of low estrogen (peak incidences in prepubertal and postmenopausal women).

2.2 Clinical Features

The diagnosis of LS is clinical, presenting as a constellation of symptoms, gross features, and clinical sequelae. In a prospective cohort study of 225 patients, the most common complaints were itching (90.2 %), burning (74.3 %), and dyspareunia (47.5 %). On examination pallor, scarring sclerosis, and atrophy were seen in half the patients. Hyperkeratosis, purpura, itching related excoriations, and erythema were also present to a lesser degree (Virgili et al. 2014). Sites of involvement include the interlabial sulci, labia minora and majora, clitoris and hood, and perineum and perianal area; mucosal sites are spared.

LS usually starts as nonspecific erythema, edema, and fragility (erosions, fissuring, purpura, and ecchymoses) and progresses to large porcelain white plaques and papules. These evolve into dry, hypopigmented, sclerotic and atrophic lesions resulting in a crinkling or cellophane paper type appearance which is pathognomonic of LS. The progressive scarring of LS can result in fusion of the labia minora, obliteration of the clitoris, and stenosis of the introitus. Although controversial, LS is considered a risk factor for invasive squamous cell carcinoma (SCC) with a reported lifetime risk of 0.3–5 %. It is not considered a premalignant lesion.

2.3 Histology

LS has been divided into an early and late stage clinically and histologically although this designation is debated due to lack of correlation between clinical duration and histologic findings. Early LS is histologically nonspecific. Findings include a lichenoid interface dermatitis and basement membrane thickening. Luminal hyperkeratosis and hypergranulosis of the adnexal structures; mild irregular, occasionally psoriasiform acanthosis; subepithelial edema; dermal homogenized collagen; and dilated blood vessels immediately under the basement

membrane may also be seen. The differential includes lichen planus, psoriasis, and Zoon's vulvitis. Late LS has a classic histologic picture of hyperkeratosis, epidermal atrophy with flattening of the rete ridges, vacuolar interface changes, loss of elastic fibers, and hyalinization of the lamina propria with or without an underlying lymphocytic infiltrate. However, a not uncommon hyperplastic variant has been described and may increase risk of development of SCC (Scurry et al. 2001; Weyers 2013). An atypical variant that may be a precursor to differentiated vulvar intraepithelial neoplasia (VIN) has also been described (Chiesa-Vottero 2006). The nonspecific features of early LS and variants of more typical late LS often make histologic diagnosis of LS difficult; clinical correlation is a must.

3 Fibroepithelial Polyp

3.1 Clinical Features

Fibroepithelial polyps (FEP) are benign indolent lesions found most commonly in the genital region of premenopausal reproductive aged women. The most common site is the vagina followed by the vulva, cervix, and extragenital sites. In the vulva, they are usually present on hair-bearing skin but involvement of the labia minora has been described. The median age in one study was 32 years, (Nucci et al. 2000) but they have been reported in a wide age range of patients, including infants and the elderly. FEP typically presents as a polypoid or pedunculated exophytic mass that is usually solitary but can be multiple with multiple lesions being seen more often in pregnant patients (Nucci et al. 2000). Symptoms include bleeding, discharge, general discomfort, and sensation of a mass. Their clinical significance stems from their gross and clinical overlap with malignant neoplasms resulting in the alternative terminology of pseudosarcoma botyroides. Biopsy or excision with histologic examination is necessary to exclude malignancy.

FEP is thought to be a hyperplastic process rather than true neoplasm. Features supporting this theory are the presence of multinucleate cells in normal adjacent tissue and the presence of estrogen (ER) and progesterone receptors (PR) in normal stromal cells (see Sect. 3.2 below). The etiology is unknown and includes origin from a regressing nevus, irritation, skin aging, and hormones. Findings to support hormones as a cause include the fact that 20 % of patients with FEP are pregnant, 10 % are on hormone replacement therapy (HRT), multiple lesions are seen in pregnant patients, and spontaneous regression after birth has been reported.

The gross appearance of FEP is variable. It is often <5 cm in size, but the literature contains examples of 10, 15, and 18.5 cm lesions (Madueke-Laveaux et al. 2013; Navada et al. 2011). Gross features range from small fleshy colored to pigmented papillomatous resembling condyloma to large pedunculated lesions which are often hypopigmented. They have also been described as edematous, mucoid, rubbery, and hard with increased vascularity and as a gelatinous cyst. The differential includes numerous benign lesions such as sebaceous cyst, condyloma, fibroid, and hymenal ring as well as malignant neoplasms.

3.2 Histology

The typical histologic features of FEP include a fibrovascular core, loose edematous stroma, prominent dilated thick walled vessels, overlying intact squamous epithelium, multinucleate stromal cells throughout including at the epithelial stromal interface, and spindle or stellate stromal cells with tapering cytoplasmic processes. The squamous epithelium may be hyperplastic, acanthotic, parakeratotic, attenuated, and rarely even ulcerated (Navada et al. 2011; Nucci et al. 2000). The lesion lacks circumscription, merging with normal tissue at the margins. The constituent stromal cell is fibroblastic/myofibroblastic by immunohistochemistry and ultrastructurally and has been shown to be

positive for ER, PR desmin, actin, and vimentin. The typical histologic appearance is easy to diagnose, but variants of these features pose diagnostic dilemmas. Focal myxoid stroma may lead to a misdiagnosis of aggressive angimyxoma (AA). However, AA is subcutaneous not exophytic and uniformly myxoid not focally. A cellular variant of FEP that has been described is particularly worrisome because it can be mistaken for sarcoma. It consists of a hypercellular stroma and can have cytologic pleomorphism, up to 10 mitoses per 10 high power fields, and atypical mitoses which can lead to a misdiagnosis of sarcoma. The presence of multinucleate cells should help exclude sarcoma as they are strictly a feature of FEP (Nucci et al. 2000).

4 Vulvar Melanosis

Vulvar melanosis (VM), also known as vulvar lentiginosis or vulvar melanotic macules, is the most common pigmented disorder of the vulva. It is a benign disorder that typically affects perimenopausal Caucasian women with a reported median age of 40–44 years in one study (Murzaku et al. 2014). It accounts for 68 % of all pigmented lesions in reproductive aged women. The typical presentation is of single or multiple asymmetric macules or patches of varying shades of tan to black color that vary in size and have poorly demarcated irregular borders. The lesions can be longstanding and grow in size (Rudolph 1990). They arise most often on mucosal surfaces with the most common sites being the labia minora followed by the labia majora (Cengiz et al. 2015). Hair-bearing skin is spared. The etiology is unknown but lichen sclerosus, human papilloma virus, and hormones have all been implicated (Murzaku et al. 2014) although one study of 23 cases failed to demonstrate common strains of HPV (Jih et al. 1999).

The most common histologic finding in VM is increased melanin pigment in the basal layer of the epidermis. It is usually accompanied by no or mild proliferation of melanocytes. If proliferation is present, it is as single cells confined to the basal layer; nesting or confluent proliferation should not be seen. Other less common findings include acanthosis, pigment incontinence with melanophages in the papillary dermis, and dendritic melanocytes at the dermal-epidermal junction. Atypia is absent or very mild (Jackson 1984; Kanj et al. 1992; Rudolph 1990; Jih et al. 1999).

Despite its benign prognosis, VM is important clinically due to its gross similarity to malignant melanoma (MM). Conservative treatment consists of baseline photography followed by sequential imaging. If melanoma cannot be excluded biopsy must be performed. Dermoscopy can also help to determine the benign nature of the lesion (Murzaku et al. 2014). VM has been proposed as a risk factor for development of MM, but no strong evidence to support this has yet been identified.

5 Nevus

5.1 Clinical Features

Vulvar nevi are present in 2 % of the female population and account for 23 % of all pigmented vulvar lesions. The median age of diagnosis is 28–33 years although a significant number can be seen in the pediatric population (<18 years of age). The most common nevus diagnosed is the typical variant that is found at other sites in the body. It is most often acquired and can be junctional, compound, or intradermal. Other variants described are congenital, dysplastic, blue, and spitz nevus. An important variant due to its histologic similarity to malignant melanoma (MM) is atypical melanocytic nevi of genital type (AMNGT). AMNGT is considered a nevus with site specific features and accounts for 5 % of vulvar nevi. Its median age of presentation is less than that of typical nevi and ranges from 17 to 26 years. A family history of dysplastic nevi or MM is more common in these patients.

Typical nevi present as symmetric macules or flat topped or dome-shaped papules with well-demarcated, regular borders. They are usually <1 cm in size and have uniform color ranging from pink, dark brown-black, and rarely blue. Common sites of involvement are the labia majora followed by the labia minora and clitoral hood.

Involvement of hair-bearing sites is less common. AMNGT present with dark pigmentation, irregular borders, and larger size (up to 2 cm in diameter). They present more often on the labia minora and have an equal distribution between mucosal and hair-bearing sites. In children, AMNGT predominate at mucosal sites.

5.2 Histology

Typical nevi are histologically identical to typical nevi anywhere else on the body. They consist of nests of cytologically bland melanocytes at the dermal-epidermal junction (DEJ) (junctional nevus), in the dermis (intradermal nevus), or both (compound nevus). Confluent or merging nests, lentiginous or pagetoid spread, mitoses, and atypia are absent. Dermal components often show maturation. AMNGT, although worrisome to the unexperienced pathologist, has a characteristic histologic appearance enabling accurate diagnosis. It is a compound nevus with well-demarcated, symmetric contours. On low power it appears large, nodular, and has increased cellularity. The junctional component consists of florid, large, irregularly distributed nests of mild to moderately atypical melanocytes that may show confluence and often have retraction artifact. These nests often are fusiform or oval shaped with their long axis parallel to the DEJ (Brenn 2011). Lentiginous and pagetoid spread into the granular layer is usually a focal finding in the center of the lesion only (Ribe 2008). Hyperchromatic and multinucleate forms may be seen as well as mitotic activity up to 2 mitoses/HPF. If melanocytic atypia is random rather than uniform, deep dermal or atypical mitoses present or necrosis seen, a diagnosis of dysplastic nevus must be ruled out.

6 Papillary Hidradenoma

6.1 Clinical Features

Papillary hidradenoma (PH), also known as hidradenoma papilliferum, is a benign neoplasm that most often affects the vulva of postpubescent Caucasian women. Rare incidents of lesions in males, other races, and extragenital sites have been reported (Scurry et al. 2009; Duhan et al. 2011). The mean age in one study of 46 patients was 52 years with a reported age range in the literature of 20–89 years (Scurry et al. 2009). The most common sites of involvement in the vulva are the labia majora (38 %) and labia minora (26 %). PH usually presents as an asymptomatic, small (2 mm to 3 cm), solitary, slow growing, dome or spherical shaped freely movable mass. It can be solid or cystic; ulcerated; pedunculated; and blue, red, or skin colored. When symptoms are present they include a nodule increasing in size, pruritus, bleeding, and very rarely tenderness. PH can rarely be multifocal; when it is, it is usually unilateral (Parks et al. 2012). The largest reported case is 8 × 5 cm (Kaufmann et al. 1987).

The histogenesis of PH was believed to be from apocrine and eccrine glands. Currently it is thought to be from mammary-like glands (MLG) in the vulva prompting some authors to advocate a name change to MLG adenoma (Scurry et al. 2009). Features supporting this theory are the analogous distribution of the lesion to vulvar MLGs, their immunophenotypic (see below) and histologic overlap, and the presence of MLGs adjacent to or in close proximity to PH on histologic sections. An association with human papilloma virus has been reported, but causation has not been proven (Vazmitel et al. 2008). PH is also thought to be a cause of Bartholin's cyst due to a reported and its typical anatomical proximity to Bartholin's duct (Docimo et al. 2008).

6.2 Histology

PH is an adenoma that arises in the dermis with no connection to the epidermis. At low power it can mimic adenocarcinoma due to the presence of a fibrotic pseudocapsule which entraps epithelium at the periphery mimicking an invasive pattern. High power shows anastomosing tubules and cystic spaces with papillary folds projecting into the lumen reminiscent of an intraductal papilloma of the breast. If tubules predominate, rare solid areas

can also be seen (Scurry et al. 2009). The tubules and papillae are composed of two cell layers: an inner layer of tall, columnar ductal cells and outer layer of flat or cuboidal myoepithelial cells. Sometimes only a single layer is present. The ductal cells can have apical snouts and faint eosinophilic cytoplasm imparting an apocrine look. Rare examples of clear, mucinous and foam cells have also been described (Scurry et al. 2009). Pleomorphism and mitoses can be present but only mildly. Ductal cells are positive for estrogen receptor (ER), progesterone receptor (PR), GCDFP-15, CK7, PanK, and EMA. Myopeithelial cells are positive for actin and p63 (Parks et al. 2012; Vazmitel et al. 2008; Shah et al. 2008).

7 Vaginal Cysts

7.1 Introduction

Vaginal cysts are clinically common lesions affecting an estimated 1/200 reproductive aged women. The cysts are often asymptomatic leading to an underestimate in not only prevalence but also a lack of pathologic examination and unfamiliarity with histologic designation. Although histologic distinction between the different cysts is not clinically important, it can be done with relative ease by understanding of embryogenesis of the vagina. The vagina is derived from mullerian, mesonephric, and urogenital sinus tissues. The common cysts can be divided into embryonic (Mullerian, Gartner's duct, and Bartholin's gland) and nonembryonic (epidermal inclusion cyst (EIC)).

7.2 Cysts of Embryonic Origin

7.2.1 Mullerian Cysts

Mullerian cysts are derived from the mullerian ducts which form the majority of the vagina. They are the most common of the benign vaginal cysts accounting for up to 44 % of cysts. They can be located almost anywhere within the vagina but are usually found in the anterolateral aspect. They range in size from 1 to 7 cm and are often asymptomatic and clinically undetectable, especially if small.

Mullerian cysts can be comprised of any of the normal mullerian tissues including endocervical (mucinous), tubal, or endometrial. The most common finding is an admixture of endocervical and tubal with admixed squamous metaplasia. Endocervical epithelium consists of tall columnar cells, basally located nuclei, and cytoplasmic and luminal mucin. Tubal epithelium consists of ciliated tubal cells with admixed tubal peg and secretory cells. Endometrial epithelium is rare and if present is usually focal. If abundant luminal mucin is present, the epithelium may become compressed or flattened making distinction between Gartner's duct cysts difficult. Confirmation of mucin with mucicarmine stain can help differentiate as Gartner's duct cysts are nonmucinous. Abundant squamous metaplasia can make distinction from EIC almost impossible but distinction is not clinically significant.

7.2.2 Gartner's Duct Cysts

Gartner's duct, or mesonephric, cysts arise from the Wolffian ducts. They are less common than their mullerian counterpart comprising approximately 10 % of benign vaginal cysts. They are often smaller than mullerian cysts and usually found along the lateral wall of the vagina. They are lined by a nonmucinous low columnar or cuboidal epithelium. They can be distinguished from mullerian cysts by the lack of ciliated epithelium, squamous metaplasia, and negative mucicarmine confirming the absence of mucin.

7.2.3 Bartholin's Gland Cysts

Bartholin's gland cysts arise due to blockage of Bartholin's duct, a 2.5 cm duct which drains into the vaginal vestibule adjacent to the hymen posteriolaterally. The gland itself is located in the posteriolateral vulva beneath the labia majora and minora. Blockage is usually a result of infection or increased viscosity of the secreted mucin. The cysts are found in the lateral introitus, range in size from 1 to 4 cm, and are usually unilateral, nontender, and asymptomatic.

Bartholin's duct is comprised of three types of epithelium: mucinous proximally and in gland acini, transitional in the middle, and squamous distally and at the entrance into the vestibule. Following this pattern, Bartholin's gland cysts can contain one, two, or all three epithelial types depending on size and location along the duct. Luminal contents consist of a clear mucoid liquid. Acute and chronic inflammations are not uncommon, and infection with resultant abscess can also be seen.

7.3 Nonembryonic Cysts

7.3.1 Epithelial Inclusion Cysts

EICs are the most common of the nonembryonic vaginal cysts. They are most often located in areas of previous surgery or trauma and are believed to be a result of traumatic inclusion of the normal vaginal mucosa. They range in size from a few millimeters to several centimeters. They are lined by stratified nonkeratinizing squamous epithelium lacking rete ridges. The lumen contains keratinaceous debris and desquamated cells. Rupture of the cyst can result in an exuberant chronic inflammatory or granulomatous reaction.

7.3.2 Endometriosis

Endometriotic cysts of the vagina can be superficial or deep. When superficial, they are located in the vaginal vault, are not associated with pelvic endometriosis, and are usually present at a site of previous surgery. Deep cysts are more common, are associated with pelvic endometriosis, and are most often located in the posterior fornix. Endometriotic cysts present as friable erythematous masses ranging in color from red to blue. Histologically, they are lined by endometrioid epithelium surrounded by endometrial stroma, hemosiderin pigment, and hemosiderin-laden macrophages.

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Malignant Vulvar and Vaginal Pathology

Grace N. Kim

Contents

Abstract

Vulvar and vaginal malignant pathology are dominated by squamous cell carcinoma and its variants. In the vulva, the majority of squamous cell carcinomas are non-HPV driven (human papilloma virus), while in the vagina, HPV infection is a key driver. In both lower genital tract sites, HPV is the main cause for low and high grade squamous intraepithelial precursor lesions. Their multifocality and synchronus and metachronous existence with lesions elsewhere in the genital tract are well-established defining characteristics. Additionally, melanomas are disproportionately prevalent in the vulva when comparing the total vulvar skin surface area to that of the entire body. Melanomas can also rarely occur in the vagina. Lastly, there are four entities distinctively found in the vulvovaginal region of the female gynecologic tract: extramammary Paget disease, aggressive angiomyxomas, embryonal rhabdomyosarcomas, and DES-related clear cell adenocarcinomas. An extensive list of different malignant entities that may occur in the vulvovaginal region are not reviewed here, but rather merely the most common.

Keywords

Human papilloma virus (HPV) • Low grade squamous lesion • Koilocyte • High grade squamous lesion • Squamous dysplasia • Differentiated-type VIN • Usual type VIN • Well-differentiated squamous cell carcinoma •

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Conventional squamous cell carcinoma • Melanoma • Basal cell carcinoma • Extramammary Paget disease • Merkel cell carcinoma • Aggressive angiomyxoma • Clear cell adenocarcinoma • Diethylstilbestrol (DES) • Embryonal rhabdomyosarcoma

1 Introduction

Vulvar cancer comprises merely 0.3 % of all new cancer cases in the United States, with an estimated 5,150 new cases in 2015. It contributes to 0.2 % of all cancer deaths with 0.3 % of women being diagnosed with vulvar cancer during their lifetime (Howlader et al. 2015). Albeit a rare malignancy of the female genital tract, vulvar cancer poses a significant clinical challenge due to its critical anatomic site at the junction of the urinary, gynecologic, and gastrointestinal systems. The associated complications, high morbidity, and multifocal recurrence are accredited to several factors, primarily the lack of effective treatment modalities which are limited currently to surgical excision, radiation, and chemotherapy. No single or combination treatment is entirely curative. Additionally, despite the well-established role of HPV infection as a driver of lower genital tract gynecologic pathology, non-HPV-driven vulvar malignancies are poorly understood and remain an area of continuing investigation.

Vaginal pathology, in comparison to the vulva, is a rare site for primary cancers. The majority of vaginal malignancies are secondary to direct extension or metastasis from nearby gynecologic sites, and merely 10–20 % of tumors involving the vagina are in fact classified as primary vaginal disease (Kurman et al. 2011). Nonetheless, HPV-driven squamous cell carcinoma is the most common primary vaginal malignancy, as it is for the vulva.

2 Vulva

The most common vulvar malignancies are squamous cell carcinomas (approximately 95 %) (Kurman et al. 2011), followed by malignant melanoma. The remainder of malignant tumors is comprised of adenocarcinomas and rarely neuroendocrine, soft tissue, and hematopoietic malignancies (Crum 2014a).

Vulvar squamous cell malignancies can be largely divided into HPV-driven and non-HPV-driven carcinomas. The HPV-driven malignancies and precursors occur in younger women (mean age 50 years), whereas non-HPV-driven carcinomas occur in an older age population (mean age 77 years). Different histologic subtypes and precursors are characteristic of each group (Kurman et al. 2011).

2.1 HPV-Driven Squamous Cell Carcinoma

HPV-driven squamous cell carcinomas of the vulva are largely associated with high risk HPV type 16. In adjacent areas, precursor lesions of intraepithelial squamous dysplasia are often seen. The precursor lesions of HPV-driven carcinomas are divided into low grade squamous intraepithelial lesion (LGSIL, historically vulvar intraepithelial neoplasia grade 1, VIN 1) and high grade squamous intraepithelial lesion (HGSIL, historically VIN 2 or 3), and both have identical histology as those found not only in the vagina, but rather the entire lower anogenital tract in both women and men. This nomenclature was widely published in 2012 through the work of The Lower Anogenital Squamous Terminology (LAST) Project and has since been recommended by the World Health Organization (WHO) for the vulva, vagina, and cervix (Darragh 2015).

Low grade squamous intraepithelial lesions can be associated with both low and high risk HPV types and tend to regress without further progression to cancer. Conversely, high grade squamous intraepithelial lesions carry a significant risk of progression to invasive carcinoma, which is three times amplified in patients who are immunosuppressed, in particular, with HIV infection. Synchronous or metachronous disease in other genital sites are not uncommon. Despite complete excision, 15 % can recur and if excisional margins are positive, the recurrence rate increases to 50 % (Crum 2014a).

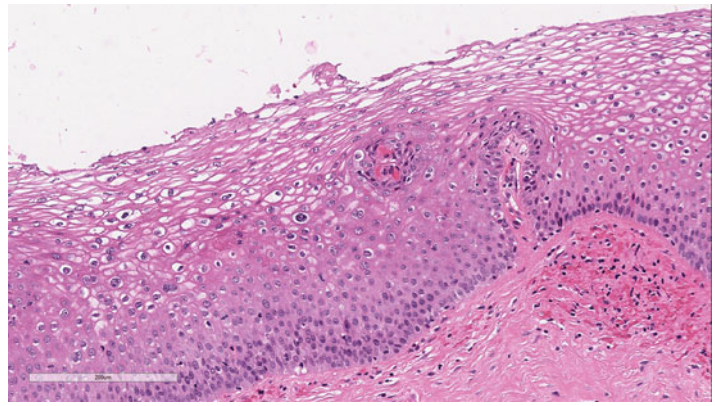

Fig. 1 Low grade squamous intraepithelial lesion (VAIN 1). Dysplastic keratinocytes involve the lower one-third of the squamous epithelium and are characterized by cellular enlargement, crowding, hyperchromasia, and increased mitoses. Koilocytes are most frequently found in the superficial third of the epithelium and have dark raisinoid or wrinkled nuclei with a well-demarcated perinuclear halo

Histologically, low grade and high grade squamous intraepithelial lesions are similar across all organ sites. Low grade squamous dysplasia is classically characterized by koilocytic atypia, which is most often found in the middle to upper portions of the squamous epithelium. Koilocytes are enlarged keratinocytes with hyperchromatic (dark), wrinkled, or raisinoid nuclei surrounded by a well-demarcated perinuclear halo. The basal layer of the squamous epithelium is also hypercellular or crowded with dysplastic keratinocytes that are enlarged and hyperchromatic. These changes in the basal layer do not extend above the bottom one-third of the squamous epithelium (Fig. 1). On the contrary, high grade squamous intraepithelial lesions have dysplastic changes occupying a greater thickness of the epithelium (at least half or more). Historically, moderate dysplasia is confined to the bottom two-thirds of the epithelium and demonstrates a superficial layer of normal squamous maturation. Severe dysplasia extends the full thickness of the epithelium and may have overlying parakeratosis (retention of nuclei in stratum corneum) or a thickened granular layer. It however lacks normal keratinization or maturation of the top layers. Additionally, mitotic figures that are normally confined to the basal layer in normal epithelium and low grade dysplasia are seen throughout the upper half of the epithelium in high grade dysplasia. Atypical forms can also be seen (Fig. 2).

When the squamous dysplasia once contained within the squamous epithelium breaks through the basement membrane into the underlying stroma, the lesion meets criteria for an invasive squamous cell carcinoma. Squamous cell carcinomas in the vulva are characterized by a variable degree of maturation or differentiation and are classified on a spectrum of well to poorly differentiated. As a general rule, less differentiation correlates with fewer areas of keratinization. Of importance, the precise terminology of well-differentiated, *keratinizing* squamous cell carcinoma in the vulva is reserved for non-HPV-related carcinomas as discussed later in this chapter. Well-differentiated keratinizing squamous cell carcinomas can be deceiving on superficial biopsies due to its histologic similarity to benign or reactive squamous epithelium, despite its deeply invasive portions. Conventional squamous cell carcinomas can be subtyped into a variety of histologic variants, including basaloid, warty, verrucous, giant cell, spindle cell, acantholytic, papillary squamous, lymphoepithelioma-like, and plasmacytoid. Basaloid carcinomas (squamous cell carcinomas of the usual type) are commonly HPV 16 related and resemble the basal, non-mature cells of the squamous epithelium often seen in the classic type of squamous high

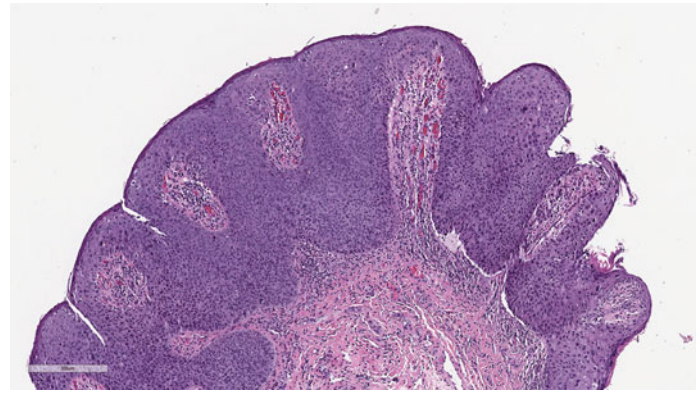

Fig. 2 High grade squamous intraepithelial lesion (VAIN 3). Dysplastic keratinocytes involve the full thickness of the squamous epithelium. The cells are crowded, hyperchromatic, and enlarged with mitoses seen in the upper two-thirds of the epithelium

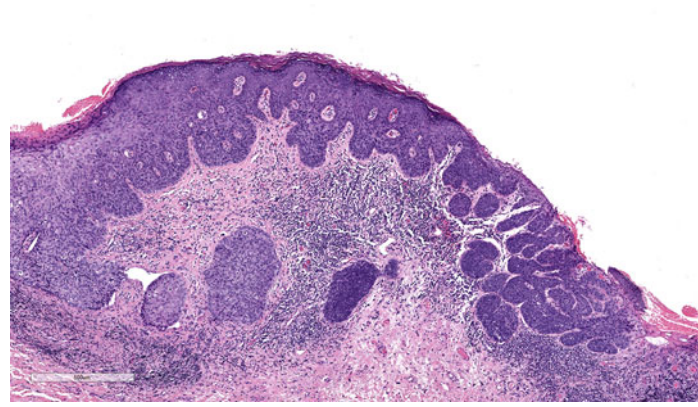

Fig. 3 Invasive moderately differentiated squamous cell carcinoma (conventional type). This basaloid subtype of invasive squamous cell carcinoma is associated with an overlying high grade squamous intraepithelial lesion (VIN 3). Nests of cells infiltrate the superficial stroma and a focus of lymph-vascular space invasion is seen on the *left*

grade dysplasia. These cells have scant cytoplasm and the tumor infiltrates the stroma as irregular nests and broad bands, cords, or cells (Fig. 3). Warty and verrucous carcinomas histologically resemble more mature squamous cells, often associated with keratinization. Warty type is characterized by areas of koilocytosis and fibrovascular cores, while the verrucous type lacks koilocytosis and fibrovascular cores, and has an exophytic papillary surface and association with HPV 6. Of importance, the verrucous type is composed of well-differentiated neoplastic cells with keratinization and absence of significant atypia or pleomorphism. Verrucous carcinoma has the best prognosis, followed by warty, and finally the basaloid type.

2.2 Non-HPV-Driven Squamous Cell Carcinoma

The most prevalent type of invasive squamous cell carcinoma of the vulva is the well-differentiated keratinizing squamous cell carcinoma. It comprises approximately 65–80 % of vulvar cases. Characteristically, keratinizing squamous cell carcinoma occurs in older women (70s) and is associated with chronic vulvar disease or vulvar dystrophy, such as lichen sclerosus and less commonly, lichen planus. Keratinizing squamous cell carcinoma is not associated with HPV infection nor the usual vulvar intraepithelial neoplasia (uVIN), but rather a vulva-specific precursor lesion termed differentiated-type VIN (D-VIN)

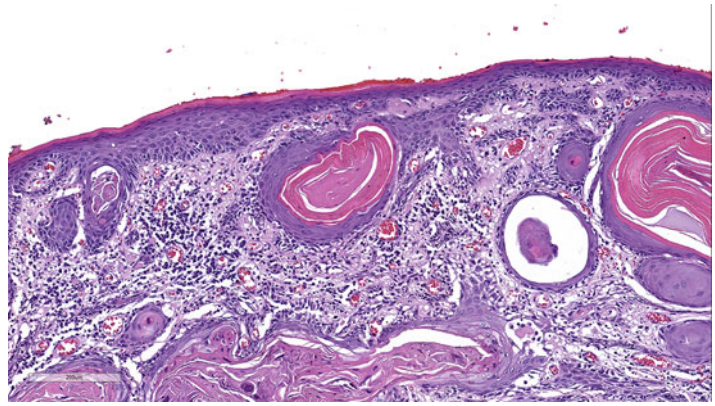

Fig. 4 Differentiated VIN (D-VIN). This precursor of non-HPV-driven squamous cell carcinoma of the vulva is a difficult histologic diagnosis. Enlarged dysplastic keratinocytes with prominent nucleoli, significant intercellular edema (spongiosis), abundant eosinophilic cytoplasm, and occasional mitoses can be seen in the parabasal and basal layers. Keratin pearls at the base of rete ridges is a characteristic finding

or VIN simplex. The risk of progression to cancer in differentiated-type VIN increases with age and the duration of the preceding chronic skin disease, and is more frequent compared to uVIN (33 % vs. 5.7 %) (Reyes and Cooper 2014).

D-VIN is a difficult histologic diagnosis, vastly different from the features of usual VIN or squamous dysplasia. D-VIN has a mitotically active basal layer with nuclear atypia characterized by dyskeratosis (abnormal keratinization), prominent nucleoli, abundant eosinophilic cytoplasm, and spongiosis (intercellular edema). These features can be seen throughout enlarged keratinocytes of the basal and parabasal layers. Distinctively, squamous keratin pearls are present at the inferior portion of the elongated and anastomosing rete ridges. Hyperkeratosis is nearly always present (Fig. 4). P53 mutations have been associated with D-VIN; however, concordance with the p53 immunostain is variable. The surrogate marker for HPV, the p16 immunohistochemical stain, would be invariably negative. Of note, HPV-driven and non-HPV-driven precursor and invasive lesions can occur simultaneously, and thus the usual type of VIN can occur alongside D-VIN or in the background of a well-differentiated keratinizing squamous cell carcinoma in 5 % of cases (Kurman et al. 2011).

Well-differentiated keratinizing squamous cell carcinoma is best characterized by dyskeratosis (abundant eosinophilic cytoplasm) and extensive keratinization that manifests as keratin pearls within the tumor. The tumor cells are large, crowded, and dark, forming invasive islands and nests, often with an irregular invasive border. In keeping with a well-differentiated squamous malignancy, intercellular bridges are well formed and histologically recognizable (Fig. 5).

2.3 Malignant Melanoma

The second most common malignant neoplasm of the vulva after squamous cell carcinoma is malignant melanoma, comprising nearly 9 % of all vulvar malignancies (Kurman et al. 2011). The vulvar skin comprises merely 1–2 % of the human body's total skin surface area; however, 3–7 % of melanomas ailing female patients occur in the vulva. Therefore, although vulvar melanomas and melanomas of the lower female genital tract are rare, there is a notable predilection of melanomas for the vulvar region. Vulvar melanomas follow an aggressive clinical course. (Mert et al. 2013; Rouzbahman et al. 2015).

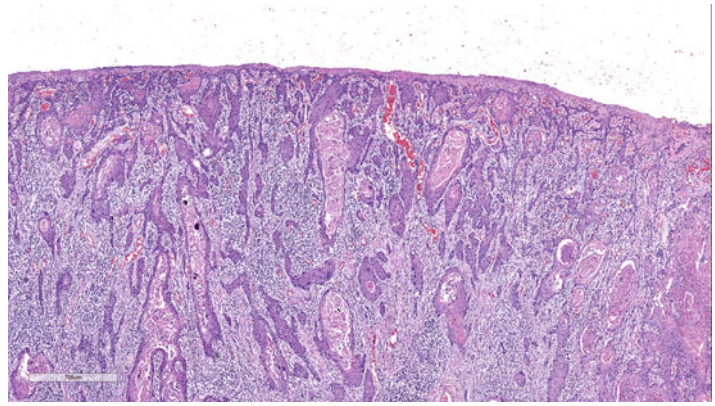

Fig. 5 Well-differentiated keratinizing squamous cell carcinoma is characterized by keratinization in the form of squamous pearls, dyskeratosis (abundant eosinophilic cytoplasm), and prominent intercellular bridges. The tumor forms islands and nests of enlarged, crowded cells with hyperchromatic nuclei and an irregular invasive border. Mitoses are common

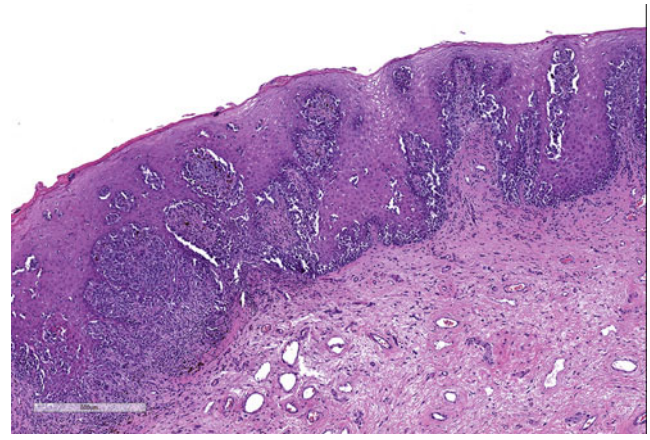

Fig. 6 Malignant melanoma. Melanoma is characterized by an increase in atypical melanocytes lining the basal layer of the epithelium with budding nests into the stroma. These lesions can be melanotic or amelanotic and can exhibit various patterns of growth, most commonly mucosal/lentiginous in the vulva. In the vagina, the nodular type is the most common.

Akin to melanomas elsewhere, melanomas of the vulva are most prevalent in women with fair skin and can be associated with precursor pigmented lesions with or without atypia. They tend to occur in an older age population (median age of 67 years at diagnosis) compared to melanomas involving cutaneous skin and are less commonly driven by BRAF mutations (Rouzbahman et al. 2015). Additionally, in contrast to cutaneous melanomas, melanomas of the vulva are not driven by exposure to UV light, and hence the incidence of vulvar melanomas has been consistent over time (Mert et al. 2013). Prognostic factors of vulvar melanoma have been studied to be similar across melanomas of different anatomic sites and include level of invasion (Clark level) and tumor thickness (Breslow). The most critical prognostic marker is lymph node involvement. Despite these analogous characteristics between cutaneous and vulvar melanomas, an optimal staging system for vulvar melanoma has yet to be consolidated (Mert et al. 2013). Additionally, histologic features that influence survival include mitotic count, surface ulceration, inflammatory response, tumor necrosis, lymph-vascular space invasion, and recurrence. Recurrences can occur in neighboring vulvar sites such as the urethra, vagina, cervix, and rectum, or metastasize to distant locations. Prognosis after recurrence is poor (Kurman et al. 2011).

Melanomas occur equally across anatomic sites of the vulva including the labia minora, labia majora, and clitoris; however, they frequently occur at the junction of the mucosa and skin in glabrous skin (smooth, non-hair bearing). The three major histologic types of melanomas arising in the vulva include the most common mucosal/lentiginous type, followed by nodular and superficial spreading types (Reichert 2012) (Fig. 6). Patterns of dermal invasion include single cells or nests and cords of atypical melanocytes with variable degrees of epithelioid, spindled, or nevoid morphology. A lymphocytic infiltrate often accompanies the invasion and an increased mitotic count signals a malignant process. With extensive variation in the histology of malignant melanocytes, melanomas have been coined as the "great mimicker," with an ability to recapitulate the histologic features of any malignant tumor at any site. Hence, a combination of melanocytic markers such as a S-100, HMB-45, Melan-A, tyrosinase, and MiTF can be employed to render the correct diagnosis. Additionally, molecular testing is currently advancing not only diagnosis, but also therapeutic options.

2.4 Basal Cell Carcinoma

This common carcinoma of the skin can also be found on the vulva, most frequently the labia majora. They account for approximately 3–5 % of vulvar malignancies unlike the very prevalent cutaneous form (Reichert, 2012), and the infiltrative type comprises nearly one-half of all cases. The histologic features are identical to basal cell carcinomas found elsewhere with a small basaloid cell population and classic peripheral palisading pattern. Wide local excision is the most common treatment modality in this often low grade lesion, although local recurrence can certainly occur.

2.5 Adenocarcinoma

Adenocarcinoma of the vulva is the rarest type of carcinoma arising in the vulva. Most adenocarcinomas of the vulva are derived from the Bartholin gland; however, due to the presence of skin appendages in the vulvar skin, adenocarcinomas of adnexal structures (sweat glands) and other vulvar components (Skene's glands) can be seen. Bartholin gland adenocarcinomas often present as a painless swelling in the area of the Bartholin glands (4 and 8 o'clock position of vulva) and can have mucinous, papillary, or rarely clear cell morphology. Of note, the Bartholin gland can harbor adenocarcinomas (40 %), but also squamous cell carcinomas (40 %), adenosquamous carcinomas (5 %), adenoid cystic carcinomas, transitional cell carcinomas, neuroendocrine carcinomas, and Merkel cell carcinoma (Crum 2014b).

Rarely, an adenocarcinoma of the vulva can be associated with an overlying extramammary Paget disease. The more common finding is that of Paget disease in isolation. Paget disease is often associated with pruritus and eczematous change and is most commonly found on the labia majora or minora. Recurrences frequently occur after local resection (33 %); however, invasion is less common. "Paget cells" are large round cells with ample cytoplasm and prominent nucleoli that are scattered as single cells or in clusters throughout the epithelium. with a greater density of cells in the basal layer. Single cells tend to float upwards towards the stratum corneum in a percolating fashion, a process traditionally described as pagetoid spread. Paget cells can often also infiltrate neighboring adnexal structures. Characteristically, Paget cells contain PAS-D positive material and immunohistochemically are positive for CK7, CAM 5.2, GCDFP-15, and carcinoembryonic antigen (CEA). In the case of S-100 positivity, melanoma must be excluded with additional immunohistochemical studies. P53 positivity in vulvar Paget cells has also been linked to metastatic disease in lymph nodes (Crum 2014a) (Fig. 7).

2.6 Neuroendocrine Carcinoma

The predominance of the already rare vulvar neuroendocrine carcinoma is mainly attributed to Merkel cell carcinoma, a neuroendocrine carcinoma of the skin. The incidence of Merkel cell

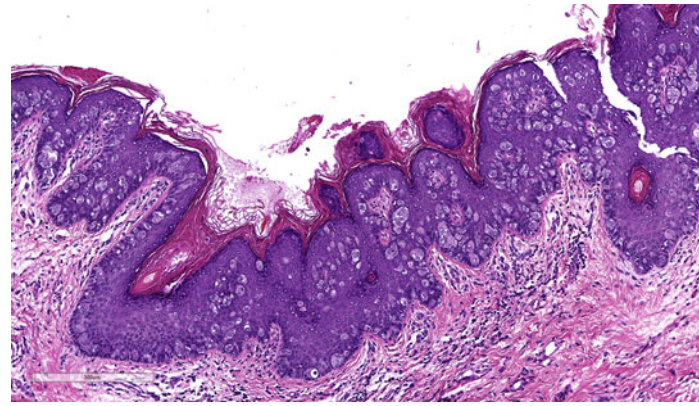

Fig. 7 Extramammary Paget disease. Extramammary Paget disease is most frequently an intraepidermal process of single cells or clusters of Paget cells. The malignant cells are round and large with abundant cytoplasm. A higher density of cells is often found at the basal layer with cells percolating to the surface. Paget disease can be associated with an underlying adenocarcinoma

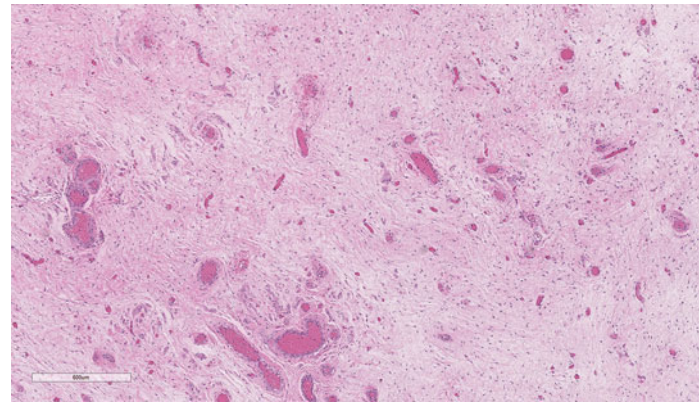

Fig. 8 Aggressive angiomyxoma. Vulvar aggressive angiomyxomas are deep soft tissue neoplasms that have infiltrative borders and vessels of varying wall thickness. The stroma is hypocellular with bland, spindle cells embedded in a background of abundant and homogenous, loose myxoid stroma

carcinomas tends to increase with age and immunosuppression. Often times they present clinically as a single surface nodule or multiple nodules and can be associated with a squamous cell carcinoma or usual type VIN.

Histologically, Merkel cell carcinoma resembles neuroendocrine tumors elsewhere (small cell carcinoma of the lung) and are comprised of small ovoid cells with scant cytoplasm and stippled chromatin to small cell carcinoma of the lung. Small polygonal cells with scant cytoplasm, granular chromatin, and small nucleoli characterize a second histologic type that resembles a low grade or well-differentiated neuroendocrine tumor previously known as carcinoid tumor. Foci of secondary glandular or squamous differentiation and adjacent intraepidermal pagetoid spread can also be seen. The prognosis of Merkel cell carcinoma is largely driven by tumor size and stage. In keeping with the universally guarded prognosis of neuroendocrine carcinomas, one-third of vulvar neuroendocrine carcinomas are linked to tumor-related mortality (Crum 2014b).

2.7 Aggressive Angiomyxoma

This low grade lesion is often found in the reproductive women involving the deep soft tissues of the vulva, vagina, or perineum and is commonly clinically mistaken for a Bartholin gland cyst. Contrary to its benign mimicker, aggressive angiomyxomas have infiltrative borders that complicate its accurate excision and propagate local recurrence. These lesions are usually large and gelatinous with histologically hypocellular and abundant, Alcian blue positive, myxoid material. Small, innocuous-appearing spindle to stellate cells are dispersed throughout, and variably sized vessels with widely patent lumens are

frequently seen in a patternless, random distribution. Entrapped smooth muscle fibers and nerve twigs, extravasated red blood cells, and mast cells can be seen. Absence of certain features, such as multinucleation, mitoses, and necrosis are also characteristic. Most importantly, the edges of the tumor are poorly circumscribed and infiltrative into surrounding adipose tissue. Aggressive angiomyxomas are positive for vimentin, estrogen receptor (ER), progesterone receptor (PR), and HMGA2 (Fig. 8).

3 Vagina

The vagina is largely a rare site of primary malignant pathology. There is no one malignant tumor that is unique to the vagina, and most vaginal malignancies are either more commonly found elsewhere in the female lower genital tract or are contributable to field effect (HPV-related), metastasis, or tumor recurrences of adjacent sites. For example, the vagina is the most common site of recurrence for endometrial carcinomas after hysterectomy. Consequentially, a few of the most common vaginal malignancies will be mentioned here, albeit the majority have been more thoroughly discussed elsewhere.

3.1 Vaginal Squamous Intraepithelial Lesions

In line with the recommendation of The Lower Anogenital Squamous Terminology (LAST) Project, all HPV-driven squamous precursor lesions regardless of site of involvement are classified as low grade squamous intraepithelial lesion (LGSIL, historically vaginal intraepithelial neoplasia or VAIN 1) or high grade squamous intraepithelial lesion (HGSIL, historically VAIN 2 or 3). The vagina, compared to the cervix and vulva, is the least common site for LGSIL and HGSIL, and vaginal lesions are most often multifocal and found in the company of other cervical or vulvar lesions, synchronous or metachronous. The majority of vaginal lesions (80–90 %) occur in the upper vagina and are associated with high risk HPV types, in particular HPV 16, regardless of the degree of dysplasia (Reichert 2012). The risk of progression in these lesions to invasive carcinoma is 5 % (Sillman et al. 1997). The histologic findings of squamous dysplasia in the vagina are no different from those found in the vulva and cervix (Fig. 2).

3.2 Squamous Cell Carcinoma

The World Health Organization (WHO) definition of primary vaginal squamous cell carcinoma includes only those carcinomas with exclusive disease in the vagina. Prior and/or concurrent invasive squamous cell carcinoma of the cervix or vulva, or any other carcinomas of adjacent sites preclude a diagnosis of primary vaginal squamous cell carcinoma. As such, vaginal squamous cell carcinoma is rare, with an incidence of 0.69/100,000 women (age-adjusted). Nevertheless, it is the most common malignant tumor of the vagina with higher incidence in black versus white women (Ferenczy et al. 2014). A predominance of vaginal squamous cell carcinomas is associated with high risk HPV infection; although, analogous to the vulva, a non-HPV-driven etiology of some squamous carcinomas is noted particularly in the lower parts of the vagina. The most common site of occurrence for squamous cell carcinoma however is the posterior, upper third vagina. Histologically, the most common variant of squamous cell carcinoma is of moderate differentiation with absence of keratinization. Other rare types, including verrucous, basaloid, warty, and papillary have been reported. Verrucous carcinoma is associated with the most favorable survival rate.

3.3 Adenocarcinomas

Adenocarcinomas comprise the majority, if not all, of the vaginal malignancies that occur in women under the age of 20 years. The most well-known adenocarcinoma is clear cell carcinoma, due to its association with diethylstilbestrol (DES) exposure in utero. DES was historically

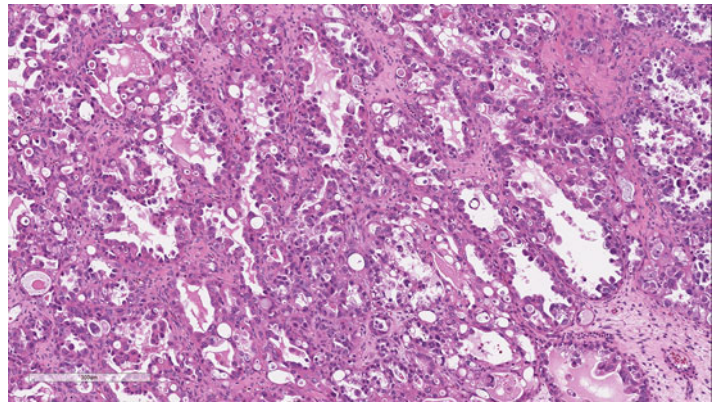

Fig. 9 Clear cell carcinoma. Clear cell carcinomas in the gynecologic tract are similar regardless of the site of involvement. These tumors are heterogeneous, with areas of papillary, solid, and tubulocystic patterns. Common histologic findings include cytoplasmic eosinophilic hyaline globules, hobnailing of atypical nuclei, fibrotic stroma, and ample clear or eosinophilic

utilized in pregnant mothers from 1940 to 1971. The daughters of mothers having taken DES during the first trimester of pregnancy have the highest risk of developing clear cell carcinoma at a young age ranging from 7 to 33 years. The risk in these women through the age of 34 is about 1 in 1000 (Melnick et al. 1987). A second risk factor for clear cell carcinoma is increased endogenous estrogen levels. Due to the widely publicized risk of DES exposure in utero, the rate of clear cell carcinoma of both the vagina and cervix has declined, and DES is no longer used under the therapeutic misconception of reducing pregnancy-related complications and miscarriages.

Clear cell carcinoma is most often found in the upper third of the anterior vaginal wall. The histology is identical to the clear cell carcinomas found elsewhere in the female gynecologic tract. Briefly, the three main patterns are papillary, tubulocystic, and solid, often with nuclear hobnailing (protrusion of nuclei from the cytoplasm), hyperchromatic nuclei, hyalinized stroma, and abundant clear to eosinophilic cytoplasm. Intracytoplasmic eosinophilic hyaline globules are characteristic, and mitotic activity and nuclear pleomorphism are underwhelming compared to other high grade carcinomas (Fig. 9).

Endometrioid adenocarcinoma is another adenocarcinoma that can be found in the vagina, with identical histologic features as those in the endometrium and ovary. They have been associated with DES exposure and also endometriosis similar to clear cell adenocarcinomas.

Lastly, mucinous carcinomas similar to the intestinal and endocervical types of the cervix can also be seen in the vagina. Little is known about the prognosis or histogenesis of this tumor in the vagina due to its rarity. Classic histomorphologic features are deferred to the description of mucinous carcinomas of the cervix.

3.4 Sarcoma

Sarcomas of the vagina are rare; however, one malignant sarcoma is of notable mention as the most common vaginal sarcoma – rhabdomyosarcoma. The three variants of rhabdomyosarcoma are as follows: embryonal, alveolar, and pleomorphic. The most common variant in the vagina is the embryonal rhabdomyosarcoma, the majority (90 %) occurring in young patients, mainly infants and children under the age of 5 years. However, these sarcomas can rarely occur in the older population.

Classically, embryonal rhabdomyosarcomas are clinically described as “grape-like” polypoid extrusions from the vagina, and are appropriately named sarcoma botryoides from the Greek term

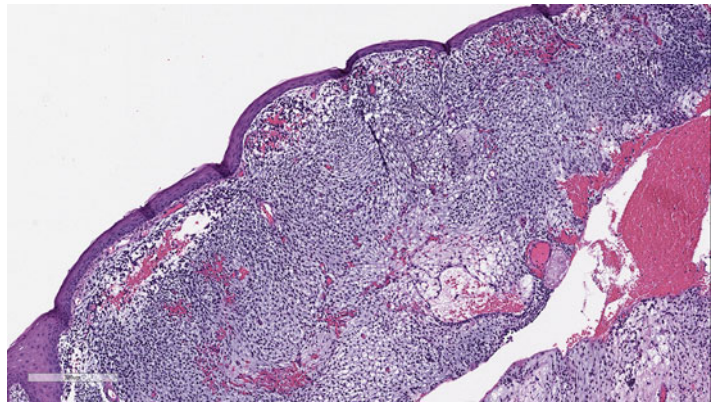

Fig. 10 Embryonal rhabdomyosarcoma. Embryonal rhabdomyosarcoma is the most common subtype of rhabdomyosarcoma found in the vagina. Clinically and histologically, they are polypoid with a densely cellular region beneath the epithelium (cambium layer). A population of hyperchromatic malignant rhabdoid cells infiltrates the deeper layers in alternating areas of cellularity in a background of myxoid material

"botryose" meaning "bunch of grapes." Histologically, these polypoid projections are covered by squamous epithelium, with or without surface ulceration, and a cambium layer immediately underneath the epithelium. The cambium layer is an area of cellular density beneath the squamous epithelium comprised of hyperchromatic nuclei. The remainder of the lesion exhibits areas of alternating hypo- and hypercellularity with round to spindle cells and scant cytoplasm. Typical rhabdoid features of an eccentrically located nucleus with abundant pink or eosinophilic cytoplasm can be seen. Cross striations of mature skeletal muscle are less common. Mitotic figures are easily found and the background stroma is usually loose and myxoid in nature. Despite historically poor clinical outcomes in young patients, current therapy combinations are highly effective with cure rates of greater than 90 % (Nucci 2014a) (Fig. 10).

3.5 Malignant Melanoma

Malignant melanomas comprise 4 % of malignancies occurring in the vagina and merely comprise 0.4 % of all melanomas. As opposed to the most common vulvar melanoma subtype, mucosal/lentiginous, melanomas of the vagina are frequently nodular. Most are pigmented with high mitotic rates, although less commonly there is absence of pigmentation or a lymphocytic response. The usual melanocytic immunohistochemical markers confirm the diagnosis. The prognosis of vaginal melanomas is extremely poor (5-year survival rate of 0–21 %), and the most significant prognostic factor is tumor size (Cao and Hirschowitz 2014).

4 Cross-References

- ▶ Benign and Malign Pathology of the Cervix
- ▶ Benign Vulvar and Vaginal Pathology

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Lesions of the Uterine Cervix

Saloni Walia and Paulette Mhawech-Fauceglia

Contents

Abstract

The fact that cervical epithelium is prone to microtrauma and its proliferation is hormonally influenced by estrogen and progesterone leads to a wide spectrum of cervical epithelial lesions. These lesions include repair, atrophy, metaplasia, infection, and inflammatory processes, as well as malignant tumors and their precursors. The uterine cervix is also unique as it is accessible to screening by Pap smears thus allowing early diagnoses of lesions. Epithelial tumors such as squamous and glandular tumors have well-characterized precursor lesions, including cervical intraepithelial neoplasia and adenocarcinoma in situ. These precursor lesions as well as epithelial malignancies are mainly caused by human papillomavirus (HPV) infection, and screening algorithms include co-testing by Pap test and HPV DNA detection. Cervical lesions are broadly classified into epithelial and mesenchymal subtypes. Epithelial tumors are by far the most common, and they are further subclassified as squamous cell carcinoma, adenocarcinoma, and neuroendocrine carcinomas. Mesenchymal tumors (sarcomas) are rare, and they are classified based on the cell of origin of the tumor. Tumors with mixed phenotypes are rare occurrences. This chapter provides a brief overview of the histological patterns of the common cervical lesions with a focus on epithelial malignant tumors and their precursors.

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1 Introduction

Uterine cervix is anatomically divided into the ectocervix lined by squamous epithelium and the endocervix lined by columnar epithelium. The transformation zone is the transition zone between the ectocervix and endocervix and is the region of high cell turnover. Precursor lesions have been identified in the uterine cervix most commonly in the transformation zone. Clinically, many benign or reactive epithelial lesions might visually mimic malignancy, and definitive diagnosis can be made only by biopsy and histologic evaluation. In addition, the uterine cervix is amenable to cytologic screening by Pap test, which has proved to be an important public health strategy leading to a decline in the overall incidence of cervical cancer. However, cervical cancer is still the fourth most common cancer among women worldwide (Ferlay et al. 2015). Cervical cancer causes significant morbidity and mortality in the developing world where universal screening by Pap test is not available. Underlying the epithelium is cervical stroma, which is composed mainly of fibroelastic tissue laced by few smooth muscle fibers. Additionally, vessels, nerves, and remnants of the Wolffian mesonephric ducts are present in the stroma. Rarely, proliferation of these mesenchymal elements leads to development of benign or malignant tumors. This chapter provides a brief overview of the cytologic and histopathologic changes characteristics of the common lesions affecting the cervix.

2 Epithelial Lesions/Tumors

2.1 Benign Lesions

Squamous Metaplasia Squamous metaplasia is the replacement of benign endocervical epithelium by benign squamous epithelium. This occurs by proliferation of the reserve cells forming immature squamous epithelium followed by maturation to benign squamous epithelium that cannot be distinguished from ectocervical epithelium (Wright et al. 2011a).

Squamous Atrophy Squamous atrophy is seen during childhood and postmenopausal years due to the absence of estrogen stimulation. It is characterized by absence of glycogen in cells and lack of surface epithelial maturation. While the cells may lose their polarity, there is residual cohesion and absence of atypia distinguishing it from in situ premalignant lesions.

Endocervical Polyps Endocervical polyps are the most common benign tumors of the cervix. They most commonly occur in women in the fourth to sixth decades of life. The initial presentation includes leukorrhea or abnormal bleeding (Wright et al. 2011a). Histologically, the most common presentation is crypts and glands lined by endocervical mucinous epithelium surrounded by fibrotic stroma containing thick-walled blood vessels (Fig. 1). Dysplastic and malignant changes are very rarely seen in endocervical polyps (Long et al. 2013).

2.2 Premalignant Squamous Cell Neoplasia/Cervical Intraepithelial Neoplasia

Squamous cell carcinoma (SCC) is preceded by a substantial period of preinvasive disease. Tumor cells lose the cohesive properties of normal cells and can be easily scraped, making them very easily accessible for screening by cytological preparations. Epithelial tumors arise from the transformation zone of the cervix, and they are known to be associated with high-risk human papillomavirus (HPV) infection which begins at the basal cells of the cervical epithelium (Walbommers et al. 1999). Due to numerous years of research, mechanism of malignant transformation of the squamous epithelium by HPV is now well characterized. HPV gene product E6 attaches to the p53 tumor suppressor protein, and

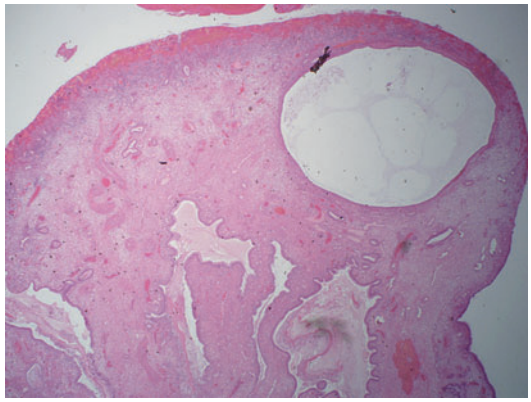

Fig. 1 Endocervical polyp: Polypoid lesion covered by endocervical mucinous epithelium and containing dilated endocervical glands, fibrotic stroma, and increased numbers of thick-walled blood vessels

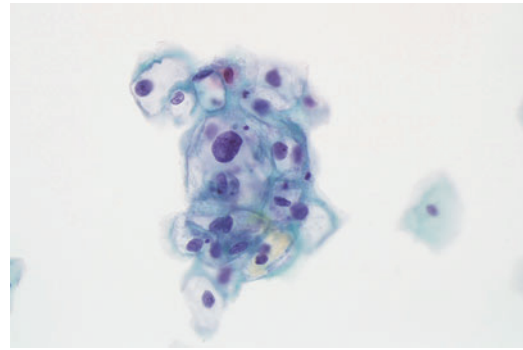

Fig. 2 LSIL: A cluster of large atypical cells is present with large irregular nuclei, clumped chromatin, perinuclear haloes, and a peripheral rim of dense cytoplasm

the E7 gene product binds the retinoblastoma gene product (pRB) causing deregulation of the host cell cycle. This leads to an increase in cellular proliferation and progressive involvement of the entire thickness of the cervical epithelium by HPV DNA (Burd 2003). HPV infection also causes disruption of cytokeratin framework in the cytoplasm of the host cell, leading to cytoplasmic clearing and perinuclear haloes (Lawson et al. 2009). Untreated infection by high-risk HPV can cause progression of cervical intraepithelial carcinoma to invasive carcinoma.

2.2.1 Cytology

On Pap smear, nuclear enlargement, hyperchromasia, irregular chromatin distribution, and clumping are the most common features of dysplastic cells. Based on the degree of these features, abnormal squamous cells can further be divided into low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). LSIL represents productive HPV infection and is self-limited in most patients. HSIL is a true neoplastic process with a capacity to progress to invasive disease if left untreated.

LSIL LSIL is characterized by at least a threefold nuclear enlargement, hyperchromasia, and variation in nuclear shape as well as contour, in the superficial or intermediate cells of the squamous epithelium. Koilocytes are characteristic cells of LSIL and have well-defined perinuclear haloes surrounded by a rim of dense cytoplasm (Fig. 2). Binucleation and multinucleation are commonly seen.

HSIL HSIL is characterized by cells that are less mature and have higher nuclear to cytoplasmic ratios than those seen in LSIL. The nuclear changes including hyperchromasia, chromatin clumping, and nuclear membrane irregularities are more severe in HSIL (Fig. 3).

HSIL can be further classified as small cell type, large cell non-keratinizing type, and large cell keratinizing type (Wright et al. 2011b). The small cell type consists of basal-type cells with very high nuclear to cytoplasmic ratios. The large cell non-keratinizing type has cells with large nuclei that form syncytial-like sheets where individual cell membranes cannot be discerned. The large keratinizing cells consist of keratinized orangeophilic atypical pleomorphic cells (Wright et al. 2011b).

2.2.2 Histology

Definitive diagnosis of intraepithelial neoplasia is made by histopathology usually on cervical biopsy specimens. The hallmark of squamous dysplasia is lack of polarity, the presence of nuclear atypia, and frequent as well as atypical mitosis. Once the diagnosis of dysplasia is made, the next step is to classify it as low-grade cervical

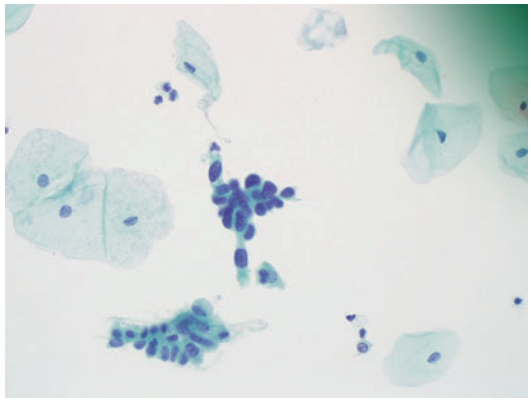

Fig. 3 HSIL: The center has an aggregate of atypical cells with high nuclear to cytoplasmic ratios, hyperchromatic nuclei, and absence of prominent nucleoli. Scattered benign squamous cells with small nuclei and abundant cytoplasm are present in the background for comparison

intraepithelial neoplasia (CIN 1) or high-grade dysplasia (CIN 2, 3) based on its severity.

Cervical Intraepithelial Neoplasia 1 (CIN1) Low-grade dysplasia is defined as dysplastic cells confined only to the lower third of the cervical squamous epithelium, signifying a mild delay in epithelial cell maturation (Martin and O'Leary 2011). In addition, it is also defined by koilocytosis which are superficial squamous epithelium cells with nuclear enlargement, atypia and perinuclear haloes (Wright et al. 2011b). There is generally a well-preserved polarity with uniform transitions to mature epithelium (Crum et al. 2011). Marked atypia and abnormal mitotic figures are not a feature of CIN1 (Fig. 4).

Cervical Intraepithelial Neoplasia 2 and 3 (CIN2 and CIN3) High-grade dysplasia is defined by dysplastic cells occupying more than half of the squamous epithelium thickness (CIN2) or by involvement of the entire squamous epithelium thickness (CIN3). Because it is difficult to differentiate between CIN2 and CIN3 and the treatment is very similar for both, these are usually referred as high-grade dysplasia (Fig. 5).

In few circumstances, differentiating between low-grade and high-grade dysplasia can be very challenging; immunohistochemistry using p16 and ki67 antibodies is used to overcome this issue.

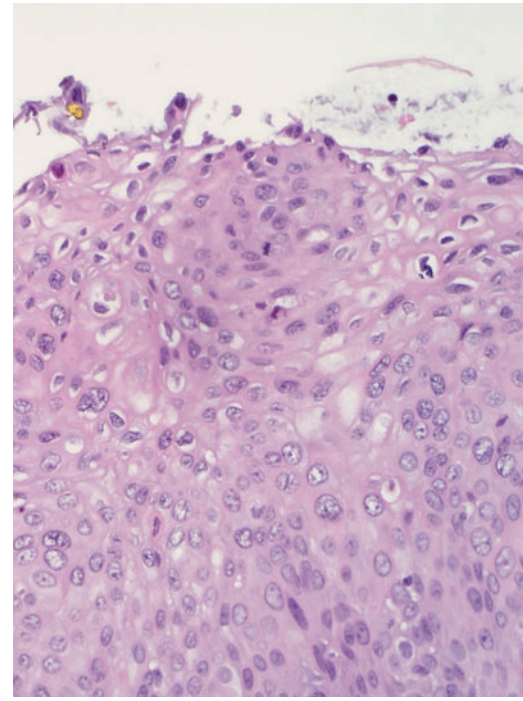

Fig. 4 CIN1: Superficial cells show koilotypic atypia with nuclear enlargement, nuclear irregularities, chromatin clumping, and sharp perinuclear haloes. Binucleation and multinucleation of cells are identified

p16 Cellular levels of p16 have been found to be upregulated in high-risk HPV-infected cervical cells. p16 is a cyclin-dependent kinase, whose downstream effect is blocked by productive HPV infection, causing accumulation and strong overexpression of p16 in infected cells (Cuschieri and Wentzensen 2008). Positive p16 immunostaining is expressed as a diffuse, strong, parabasal nuclear staining pattern and is suggestive of a transforming infection by high-risk HPV and accompanied CIN2/3. The low-grade lesions which are associated with low-risk HPV infections tend to exhibit a focal and scattered weak blush of p16 rather than the diffuse strong granular staining pattern typical for HSIL (Martin and O'Leary 2011).

Ki67 Ki67 is an antigen that identifies proliferating cells. MIB-1 is a monoclonal antibody that detects this antigen in the cell's nuclei in paraffin tissue sections. Positive MIB-1 staining in parabasal cells of the squamous epithelium is found under normal conditions. Distinction of a CIN2/3 from

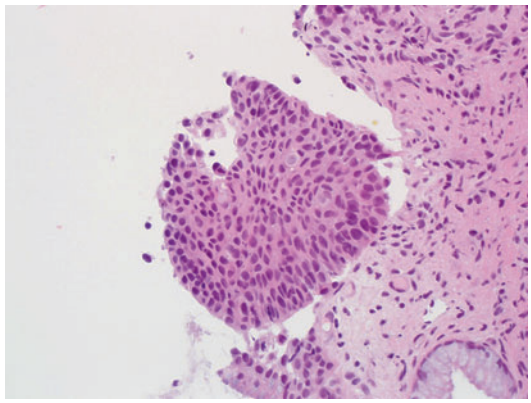

Fig. 5 CIN3: Large atypical cells that have lost their polarity extend to the full thickness of the epidermis with frequent Mitosis and absence of stromal invasion

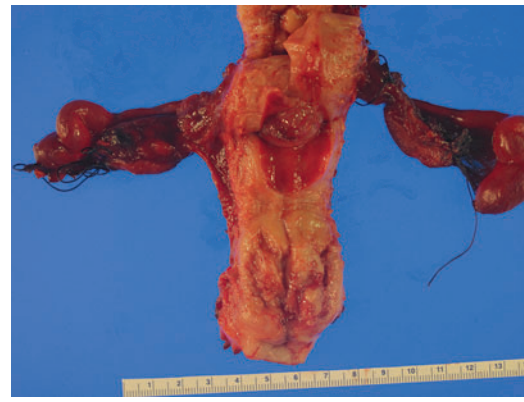

Fig. 6 Gross appearance of invasive squamous cell carcinoma: Irregular large tumor is seen to invade the endocervical mucosa. There is obliteration of the endocervical canal and invasion of the cervical stroma

nonneoplastic epithelium is based on the presence of MIB-1-positive cells in the middle and upper thirds of the epithelium. A high index of Ki67 nuclear staining and diffuse p16 nuclear and cytoplasmic expression involving most of the mucosal thickness are highly suggestive of high-grade dysplasia.

2.3 Invasive Squamous Cell Carcinoma

Histologically, the hallmark of invasive squamous cell carcinoma (SCC) is stromal invasion by malignant cells leading to a stromal loosening, desmoplasia, and/or increased epithelial cell cytoplasmic eosinophilia (Kurman et al. 2014). Squamous cells breach the basement membrane and invade the stroma. Malignant squamous cells are characterized by high nuclear/cytoplasmic ratio, hyperchromatic nuclei, pink cytoplasm, and frequent mitotic figures. On the other hand, desmoplastic reaction is defined by loose somewhat edematous stroma, associated with chronic and acute inflammation surrounding tumor cells (Kurman et al. 2014) (Fig. 6).

2.3.1 Microinvasive Squamous Cell Carcinomas (MicrSCCs)

Based on the International Federation of Gynecologic Oncologists (FIGO), they are defined as microscopic tumors that invade to less than 5 mm into the depth of the epithelium and have a horizontal span of less than 7 mm. However, the Society of Gynecologic Oncologists definition uses a depth of invasion of less than 3 mm and an absence of lymphovascular invasion (Cebellos et al. 2006). MicrSCCs are associated with excellent long-term survival after surgical treatment.

2.3.2 Invasive Squamous Cell Carcinoma

Invasive SCCs can have multiple morphological variations and may present as sheetlike growth or single-cell invasion.

Conventional SCC Conventional SCCs are classified as keratinizing or non-keratinizing types. Keratinizing SCC shows the presence of keratin pearls, cytoplasmic keratinization, and/or keratohyaline granules (Kurman et al. 2014). The tumor cells have eosinophilic cytoplasm and prominent intracellular bridges (Fig. 7). Non-keratinizing tumors consist of polygonal squamous cells with intracellular bridges that lack the presence of keratin pearls. SCC are graded into three grades: well (G1), moderately (G2), and poorly (G3) carcinomas based on degree of atypia, mitotic figures, and presence of keratin pearls. Grading SCC seemed to have an impact on patient prognosis and outcome. Other variants of SCC include the following:

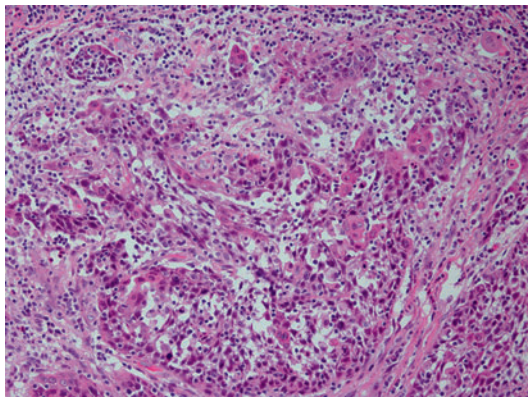

Fig. 7 Invasive SCC: Large irregularly arranged cells with keratin formation, large nuclei, and prominent nucleoli are seen invading the cervical stroma with a prominent desmoplastic response

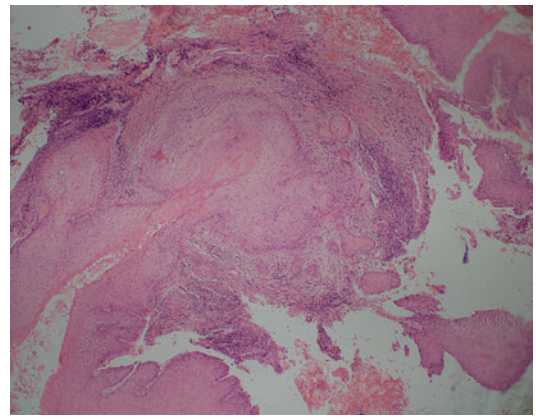

Fig. 8 Verrucous SCC: This is a well-differentiated SCC seen to be invading the cervical stroma with broad pushing borders

Verrucous Carcinoma Verrucous carcinoma is a rare variant of the cervical SCC that is frequently misdiagnosed as condyloma acuminatum on a superficial cervical biopsy. It is a well-differentiated exophytic SCC, and the epithelium lacks significant atypia or mitosis. The base of the tumor invades the underlying stroma with broad and expansile pushing borders (Fig. 8). These are differentiated from condyloma acuminatum by the absence of fibrovascular cores in the papillary cores of the verrucous carcinoma (Degefu et al. 1986; Jennings and Barclay 1972). They are very challenging and often missed on biopsy specimen. Verrucous carcinomas are locally aggressive and only rarely metastasize.

Warty/Condylomatous Squamous Cell Carcinoma This is a variant of SCC with architectural similarities to condyloma acuminata. Microscopically koilocytic atypia is present in the tumor cells, and, however, the base of the tumors shows typical changes of SCC with stromal invasion (Wright et al. 2011b; Kurman et al. 2014).

Basaloid SCC Basaloid SCC is an aggressive variant of SCC formed of nests or cords of small, intermediate, or large basaloid cells which are hyperchromatic and have high nuclear to cytoplasmic ratios. The characteristic feature is the presence of peripheral palisading of the tumor cells (Grayson and Cooper 2002). High mitotic rate and geographical necrosis are frequently seen (Kurman et al. 2014). As these tumors are very aggressive, it is important to distinguish it from other solid tumors of the cervix, including adenoid cystic carcinoma, adenoid basal carcinoma, and small cell neuroendocrine carcinoma.

Lymphoepithelioma-Like Carcinoma This variant has distinct morphological appearance and is considered less aggressive than conventional SCC. The tumor is well circumscribed and consists of undifferentiated tumor cells present in sheets or nests. The tumor cells have large uniform vesicular nuclei with prominent nucleoli, scant cytoplasm, and poorly defined cell membranes. The mitotic rate is high. Tumor cells are surrounded by a dense inflammatory infiltrate consisting of lymphocytes and plasma cells (Martorell et al. 2002). A role of Epstein-Barr virus (EBV) infection is suggested in the pathogenesis of this variant.

Papillary SCC/Papillary Transitional Cell Carcinoma The tumor is architecturally composed of narrow or broad papillae that contain cores of edematous fibrous stroma with prominent capillaries and stromal inflammation. The papillae are covered with a layer of cytologically dysplastic cells resembling high-grade squamous intraepithelial neoplasia (Mirhashemi et al. 2003).

The invasive part of the tumor resembles conventional SCC. These are aggressive lesions and may be difficult to differentiate from papillary squamous cell carcinoma in situ on biopsy sections.

2.4 Glandular Lesions of the Cervix

Adenocarcinomas are cervical epithelial tumors that show glandular differentiation. There has been a small increase in the incidence of endocervical adenocarcinoma over the past few decades. Most cervical adenocarcinomas are detected within the first three decades of life. Similar to squamous carcinoma, adenocarcinomas are linked to HPV infection; however increased prevalence of HPV type 18 and variants of HPV type 16 are found in adenocarcinomas compared to squamous cell carcinomas. Around 50 % of endocervical tumors have a concurrent squamous lesion (Wilbur 2016). Intraepithelial neoplasia is a precursor lesion to invasive adenocarcinoma and is referred to as adenocarcinoma in situ (AIS). It may involve both the endocervical surface and endocervical glands.

2.4.1 Adenocarcinoma In Situ (AIS)

Preinvasive endocervical lesions are usually asymptomatic, and they are not easily visible by colposcopy as they lie high up in the endocervical canal. On Pap smears, adenocarcinoma in situ is identified as three-dimensional clusters or crowded group of cells with hyperchromatic nuclei and features of glandular differentiation which may include the presence of columnar cells, rosettes, or feathering of the nuclei at the edges (Cibas 2014). The neoplastic cells also demonstrate pseudostratification and inconspicuous nucleoli. Mitosis and apoptotic debris are frequently seen.

On histopathology, AIS is characterized by architecturally preserved endocervical glands lined by atypical columnar cells. The atypical cells have increased nuclear to cytoplasmic ratios, usually show mucin depletion, and some glands have abrupt transition between benign and malignant endocervical epithelium. The cytological features of pseudostratification, lack of prominent nucleoli, multiple mitoses, and apoptotic bodies should also be seen (Fig. 9).

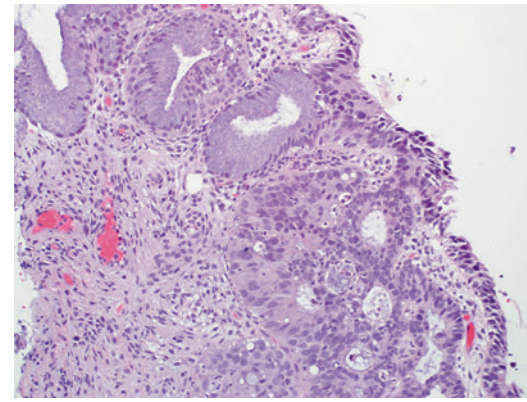

Fig. 9 AIS: There is sudden shift from benign endocervical glands with small basal nuclei and abundant cytoplasm to atypical glands with pseudostratification of epithelial cells with loss of polarity, nuclear hyperchromasia, and depletion of intracellular mucin. Atypical cells are limited to the ductal epithelium, and no invasion is identified

The three most frequent subtypes are endocervical AIS, intestinal AIS, and endometrioid AIS. The endocervical type is the most common subtype and has atypical columnar cells with eosinophilic cytoplasm and depletion of mucin. Intestinal AIS is characterized by the presence of goblet cells. The endometrioid variant resembles proliferative endometrium and is characterized by cells with small nuclei and dense eosinophilic cytoplasm lacking mucin. The stratified mucin-producing intraepithelial lesion (SMILE) variant is a relatively rare subtype and has the following features: squamoid growth pattern along with intracellular mucin (Park et al. 2000). The mucin is present in the form of discrete vacuoles or as cytoplasmic clearing throughout all the layers (Kurman et al. 2014). In addition, cytological features of AIS with nuclear hyperchromasia, nuclear crowding, mitoses, and apoptotic bodies are present. AIS should be distinguished from benign lesions such as tubal and endometrioid metaplasia. This is extremely important due to their benign nature necessitating no further therapy for the latter and the need for conization and possible further therapy for the former. The major finding in tubal and endometrioid metaplasia is

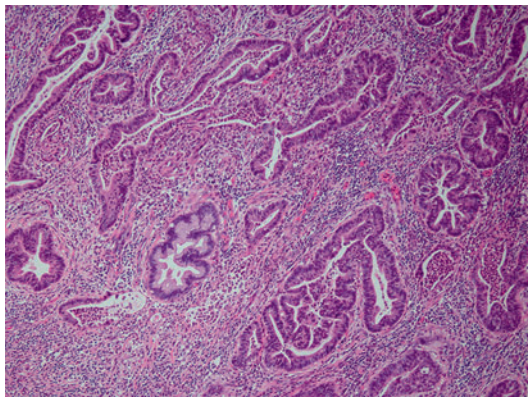

Fig. 10 Adenocarcinoma: Irregular large invasive glands lined by atypical cells showing pseudostratification and hyperchromatic nuclei surrounded by desmoplastic stroma

the presence of bland-looking columnar cells lacking hyperchromasia and nucleoli, ciliated brush in the glands lumen, and absence of significant mitosis.

Immunohistochemical studies using p16 and Ki67 are rarely used, and they act as markers of productive high-grade HPV infection and rapid cellular proliferation, respectively.

2.4.2 Invasive Adenocarcinoma

Invasive adenocarcinoma is characterized by the presence of cytologically and architecturally abnormal glands invading into the cervical stroma. On Pap smears, endocervical adenocarcinoma is usually seen as sheets of atypical cells with large round nuclei, prominent nucleoli, abundant cytoplasm, and tumor diathesis. Histopathologically, endocervical adenocarcinoma is further divided into multiple subtypes including conventional endocervical adenocarcinoma, endometrioid, adenocarcinoma, mucinous adenocarcinoma, clear cell adenocarcinoma, serous adenocarcinoma, and mesonephric adenocarcinoma (Loureiro and Oliva 2014).

Conventional Endocervical Adenocarcinoma (CEA) CEA exhibits a complex architectural glandular pattern including branching, cribriform, and papillary patterns. The lining epithelial cells are usually mucin poor and show pseudostratification with elongated hyperchromatic nuclei and prominent macronucleoli. These cells have an apical zone of eosinophilic cytoplasm. Apoptotic bodies are easily seen. Desmoplastic reaction is seen surrounding the invasive glands (Fig. 10). The stroma may show the presence of mucin pools (Kurman et al. 2014; Loureiro and Oliva 2014). Villoglandular papillary carcinoma is a well-differentiated variant of CEA that is characterized by the presence of tall and thin surface papillae lining spindled cells forming a fibrous core. The papillae are lined by endocervical-type cells. The invasive portion of the tumor is composed of elongated branching glands invading the stroma (Young and Clement 2002).

Endometrioid Endocervical Adenocarcinoma It is a rare subtype characterized by tubular glands lined by cells that lack mucin, resembling endometrial cells, and has fewer mitosis and apoptotic bodies than the usual endocervical adenocarcinoma.

Mucinous Endocervical Adenocarcinoma These are characterized by the presence of mucin-rich cells, in contrast to mucin-depleted cells of the usual endocervical adenocarcinoma (Young and Clement 2002). These may resemble gastric epithelium, intestinal epithelium, or signet ring type. Gastric-type endocervical adenocarcinoma is rare and thought to be unrelated to HPV (Carleton et al. 2015). On morphology, the tumor cells have abundant eosinophilic cytoplasm, intracellular mucin, and distinct cell membranes. The neoplastic glands are present deeper than the expected level of benign endocervical glands and are architecturally more irregular, angulated, dilated, cribriform, or fused in appearance (Kurman et al. 2014). Desmoplasia may be noted in the cervical stroma surrounding the neoplastic glands. Adenoma malignum refers to the well-differentiated gastric-type adenocarcinoma. The intestinal-type mucinous adenocarcinoma has cells similar to the epithelial cells of the large intestine and may frequently have goblet cells. This type is frequently HPV and p16 negative (Wright et al. 2011b). Signet ring cells are formed when the intracellular mucin pushes the nucleus to the periphery and are usually seen in mixed adenosquamous carcinoma (Loureiro and Oliva 2014).

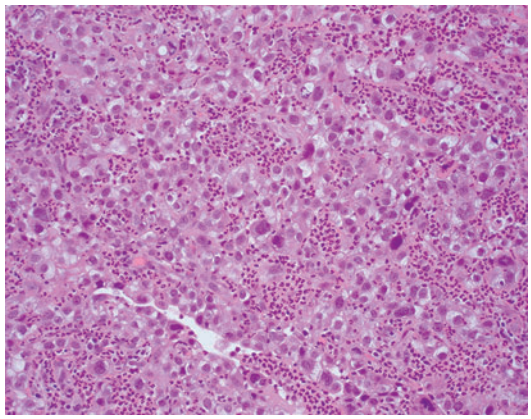

Fig. 11 Glassy cell variant: There are large polygonal atypical cells with ground-glass-like cytoplasm, large vesicular nuclei, and prominent nucleolus. The stroma shows marked infiltration by inflammatory cells

Clear Cell Endocervical Adenocarcinoma This subtype may have tubulocystic, solid, or papillary architecture. The malignant cells have clear cytoplasm and may show hobnailing. There is a historically an association between the presence of diethylstilbestrol exposure in utero and clear cell carcinoma of the ectocervix (Loureiro and Oliva 2014).

Serous Endocervical Adenocarcinoma It is very rare, and a diagnosis of primary serous cervical carcinoma should be made only after exclusion of origin in other organs of the female genital tract or the peritoneum (Loureiro and Oliva 2014). These have a distinct architecture, composed of papillae, with cellular budding and psammoma bodies (Kurman et al. 2014; Nofech-Mozes et al. 2006). The cells are markedly pleomorphic with high-grade atypia and frequent mitotic figures (Kurman et al. 2014).

Mesonephric Endocervical Adenocarcinoma It is an uncommon neoplasm that is not associated with HPV infection (Nofech-Mozes et al. 2006). These have a variety of architectural patterns including tubular, ductal, retiform, solid, or sex-cord like. The malignant cells are cuboidal, lack mucin, and may contain eosinophilic hyaline secretion in their lumen (Kurman et al. 2014).

Other rare epithelial tumors include adenosquamous carcinoma, glassy cell carcinoma, and adenoid cystic carcinoma (Fig. 11).

2.5 Neuroendocrine Tumors

Neuroendocrine tumors are very rare cervical epithelial tumors that range from well-differentiated (carcinoid tumors) to moderately differentiated (atypical carcinoid tumors) to poorly differentiated (small cell and large cell neuroendocrine carcinoma) neoplasms. They are also associated with HPV infection, and similar to cervical adenocarcinoma, HPV 18 has been more frequently observed in association with neuroendocrine neoplasms. Poorly differentiated neuroendocrine tumors are frequently associated with conventional neoplasms including CIN, SCC, AIS, and adenocarcinoma. It is postulated that HPV infection of the basal cell of the cervical epithelium may cause the pluripotent basal cell to differentiate along different cell lines, leading to coexistence of these epithelial tumors.

Poorly differentiated neuroendocrine tumors are aggressive and have a high propensity toward nodal metastasis.

Carcinoid Tumors Carcinoid tumors are well to moderately differentiated and have an organized architecture showing trabecular, solid, or cord-like pattern, with rosetting. The cells are monomorphic and lack atypia, frequent mitosis, and necrosis. The nuclei are small with finely granular chromatin, and the cytoplasm may contain neurosecretory granules. Atypical carcinoids resemble typical carcinoids architecturally; however they have more mitoses, nuclear atypia, and necrosis compared to the typical carcinoids (Rouzbahman and Clarke 2013).

Small Cell Neuroendocrine Tumors They are poorly differentiated and lose the organized architecture seen in carcinoids. On histology, these are highly cellular, formed of monomorphous small cells with high nuclear to cytoplasmic ratios, finely stippled chromatin, and inconspicuous nucleoli. Cells display prominent overlap or

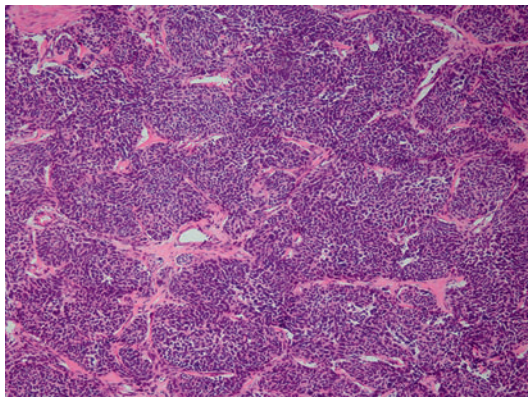

Fig. 12 Small cell carcinoma: Sheets of hyperchromatic small cell with high nuclear to cytoplasmic ratios, cell overlap, and molding are identified. The nuclear chromatin is finely stippled, and there is absence of prominent nucleolus

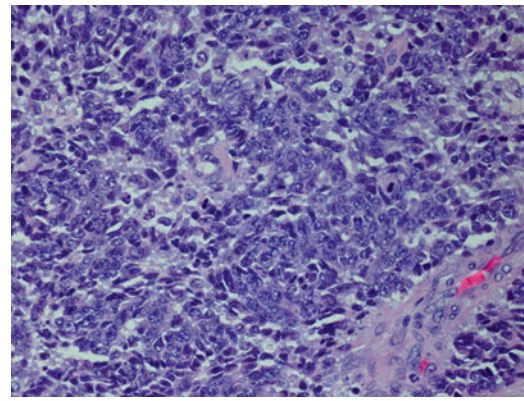

Fig. 13 Large cell carcinoma: Sheets of large cells with vesicular nuclei, prominent nuclei, and moderate cytoplasm are seen. Mitosis is frequently seen

nuclear molding, and geographic tumor necrosis is present. Mitotic rate is high, and lymphovascular space invasion is frequent (Rouzbahman and Clarke 2013) (Fig. 12).

Large Cell Neuroendocrine Carcinomas They have large cells with abundant cytoplasm, large nuclei, prominent nucleoli, and a high mitotic rate (Kurman et al. 2014) (Fig. 13).

Immunohistochemical studies using synaptophysin, chromogranin, CD56, and neuron-specific enolase may be needed for confirmation of diagnosis of neuroendocrine differentiation.

3 Mesenchymal Tumors

Sarcomas of the uterine cervix are uncommon tumors. A brief description of the common sarcomas of the cervix is provided below.

Leiomyosarcoma As primary cervical leiomyosarcomas (LMS) are rare, an attempt should be made to exclude the lower uterine segment as the site of origin (Fadare 2006). On morphology, these are spindle cell tumors with variable atypia, tumor necrosis, and atypical necrosis. They resemble similar tumors at the uterine corpus (Kurman 2014). Histological subtypes include epitheloid, myxoid, clear cell, and xanthomatous types (Crum et al. 2011). LMS should be distinguished from the most common benign mesenchymal tumors such as leiomyoma. The absence of tumor necrosis, atypia, and mitotic figures favors the latter. Immunohistochemistry is necessary to confirm the diagnosis of smooth muscle origin of LMS which usually express smooth muscle actin, desmin, and h-caldesmon.

Alveolar Soft Part Sarcoma These tumors have nested patterns that architecturally resemble alveoli of the lung (Feng et al. 2014). The malignant cells are large monomorphic, polygonal with eosinophilic cytoplasm, growing in a solid or dyscohesive pattern. The diagnosis is confirmed by cytogenetics as this tumor shows t(X;17) translocation resulting in *ASPL/TFE3* gene fusion.

Rhabdomyosarcoma Rhabdomyosarcomas are malignant tumors with skeletal muscle differentiation and are further classified as embryonal, alveolar, and pleomorphic subtypes. Alveolar rhabdomyosarcoma is most commonly seen and consists of malignant cells arranged in an alveolar pattern surrounded by fibrous tissue with vascular tissue. The tumor cells contain large hyperchromatic nuclei and can be large polygonal or small spindle shaped (Rivasi et al. 2008). Cytogenetic abnormalities t(2;13) (q35;q14), resulting in

the fusion genes *PAX3-FKHR* and the less frequent t(1;13)(p36;q14), with fusion of *PAX7-FKHR*, are seen in majority of the cases.

Angiosarcoma Angiosarcomas are aggressive tumors consisting of interconnecting vascular channels lined by cuboidal cells with large atypical nuclei and high nuclear to cytoplasmic ratios. Tumor cells are positive for CD31, CD34, ERG, and factor VIII-related antigen by immunohistochemistry. Rarely, malignant peripheral nerve sheath tumor, primary malignant melanoma, germ cell tumors, lymphoid, and myeloid malignancies may arise in the cervix.

4 Mixed Epithelial and Mesenchymal Tumors

Mixed epithelial and mesenchymal tumors containing adenosarcoma and carcinosarcoma may be present. In adenosarcoma, a benign epithelial component is associated with a malignant mesenchymal part, while in carcinosarcoma, both the epithelial and mesenchymal components are malignant.

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Pathology of the Uterine Corpus

Helena Hwang

Contents

Abstract

Endometrial cancer is the fourth most common cancer in women in the United States. Endometrial carcinomas can be divided into two types based primarily on association with excess estrogen. Endometrioid adenocarcinoma is the prototypical type 1 endometrial carcinoma, well known for its association with excess estrogen. It is the most common uterine malignancy and usually occurs in postmenopausal women. Endometrial hyperplasia is widely recognized as a non-obligate precursor to endometrioid adenocarcinoma. Type 2 endometrial carcinomas are not associated with excess estrogen and include serous and clear cell carcinomas. A wide variety of other neoplasms occur in the uterus. More common entities include biphasic tumors like malignant mixed Mullerian tumors (MMMT) and mesenchymal malignancies such as endometrial stromal sarcoma and leiomyosarcomas. More rare uterine tumors include perivascular epithelioid cell tumor (PEComa), primitive neuroectodermal tumor (PNET), lymphoma, and gestational trophoblastic disease.

Keywords

Endometrial hyperplasia • Endometrial intraepithelial neoplasia • Endometrioid adenocarcinoma • Clear cell carcinoma • Endometrial stromal sarcoma • Leiomyosarcoma • Malignant mixed Mullerian tumor •

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Gestational trophoblastic disease • Hydatidiform mole

1 Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the United States, of which endometrioid adenocarcinoma is the most common type. Endometrial hyperplasia is a widely recognized non-obligate precursor to endometrioid adenocarcinoma. Other types of endometrial carcinomas include serous, clear cell, and malignant mixed Mullerian tumors (MMMT), among others. In addition to carcinomas, many different neoplasms can be found in the uterus. Leiomyoma is the most common tumor of the uterus; mesenchymal malignancies, such as endometrial stromal sarcoma and leiomyosarcomas, are less common. Other tumors that can be encountered in the uterine corpus include perivascular epithelioid cell tumor (PEComa), primitive neuroectodermal tumor (PNET), lymphoma, and gestational trophoblastic disease, all of which are rare. In this chapter, the histology of various tumors of the uterine corpus will be described with explanations of workup and differential diagnosis.

2 Histology of Normal Uterine Corpus

The uterine corpus consists of the endometrium, myometrium, and serosa. The endometrium is divided into stratum functionalis, the superficial portion that sheds into the uterine cavity, and stratum basalis, the deeper portion that abuts the myometrium. The appearance of the stratum functionalis varies depending on the time of the menstrual cycle while the basalis remains constant. Normal endometrium is composed of glands and stroma in an approximately 1:1 ratio. The stroma consists of a uniform population of small, round to spindled blue cells. In the proliferative phase, the glandular epithelium shows columnar cells with pseudostratification, and the stroma ranges from cellular to edematous. Both the glands and stroma show mitoses. The hallmark of secretory phase is vacuoles in glandular cells. Secretory phase shows features distinct enough to date day by day. In late secretory phase, a sawtooth pattern, the presence of neutrophils, and stromal predecidualization are seen. In predecidualization, the stromal cells become larger, plumper, and rounder, showing increased eosinophilic cytoplasm. During menstruation, glandular and stromal breakdown is seen with fibrin and necrosis. In postmenopause, the endometrium becomes atrophic, characterized by glands with a single layer of cuboidal or flat epithelial cells without stratification and without mitoses.

The myometrium is the thickest layer of the uterus and is composed of smooth muscle cells. The serosa is the outermost layer of the uterus and is composed of a single layer of mesothelial cells.

3 Endometrioid Adenocarcinoma Precursors

3.1 Endometrial Hyperplasia

Endometrial hyperplasia is a well-known non-obligate precursor to endometrioid adenocarcinoma. The most widely used classification system for endometrial hyperplasia is one that the World Health Organization (WHO) adopted in 1994, dividing endometrial hyperplasia into four categories: (1) simple hyperplasia, (2) complex hyperplasia, (3) simple hyperplasia with atypia, (4) and complex hyperplasia with atypia. In 2014, WHO revised this system, simplifying classification into two categories: hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia (EIN) (Kurman et al. 2014). Both systems will be described below.

In endometrial hyperplasia, proliferative type endometrium is seen with an increased gland-to-stroma ratio with architectural complexity. Architectural complexity is defined as irregularity in gland size and shape. In simple hyperplasia, glandular crowding is present with mild to moderate architectural complexity, sometimes with cystic

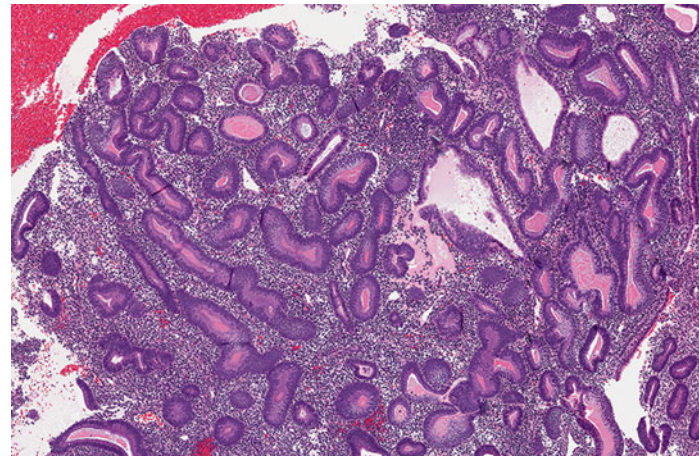

Fig. 1 Simple hyperplasia without atypia. Glandular crowding with proliferative type endometrial glands showing irregular shapes

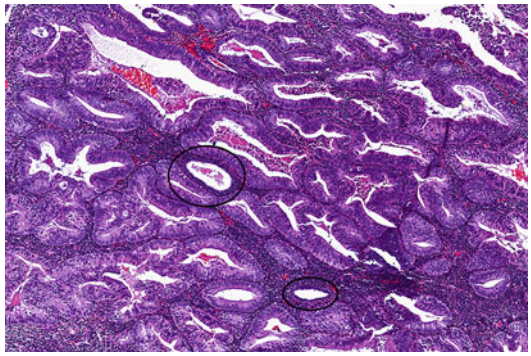

Fig. 2 Endometrial intraepithelial neoplasia (EIN). Marked glandular crowding with architectural complexity and enlargement and rounding of cells. Note that background glands (*circled*) are different from the neoplastic glands

glands (Fig. 1). Complex hyperplasia shows increased glandular crowding and increased architectural complexity, including branching and outpouching of glands. Atypia refers to cytologic atypia defined by nuclear enlargement, loss of polarity with rounding of the nucleus rather than ovoid nuclei, irregular nuclear borders, pleomorphism, and prominent nucleoli. Among the four categories, simple hyperplasia without atypia and complex hyperplasia with atypia are most commonly seen while simple hyperplasia with atypia is very rare.

While widely used, this classification system is known to suffer from interobserver variability with suboptimal reproducibility. The binary system proposed in the most recent WHO aims to reduce interobserver reproducibility by simplifying classification. It is also based on the finding that cytologic atypia is the most significant factor in progression to endometrioid adenocarcinoma. The majority of hyperplasia without atypia regresses while 8 % of simple hyperplasia with atypia and 29 % of complex hyperplasia with atypia progress to endometrioid adenocarcinoma (Kurman et al. 1985).

3.2 Endometrial Intraepithelial Neoplasia

Endometrial intraepithelial neoplasia (EIN) is a monoclonal precursor lesion that was originally identified based on morphometric analysis and finding genetic alterations similar to that seen in grade 1 endometrioid adenocarcinomas (Mutter et al. 2000). The histologic criteria for EIN are (1) gland-to-stroma ratio greater than 1:1, (2) cytology of cells in lesional area is different from background glands or cytology is clearly abnormal, (3) greater than 1 mm focus, (4) and exclusion of benign mimics such as polyps, basalis, disordered proliferative endometrium, metaplastic change, and carcinoma (Fig. 2).

While most cases of atypical hyperplasia would fit the definition of EIN, these two categories are not interchangeable, as cases previously diagnosed as simple hyperplasia without atypia and complex hyperplasia without atypia have been reclassified as EIN.

The differential diagnosis of endometrial hyperplasia includes, but is not limited to, endometrial polyps, disordered proliferative endometrium, stratum basalis, metaplastic change, and endometrioid adenocarcinoma. Endometrial polyps may show disorganized glands resembling hyperplasia. Recognizing characteristic features of endometrial polyps such as thick-walled vessels and fibrotic stroma or polypoid architecture can help to distinguish between the two, although in an endometrial biopsy, distinction can be challenging at times. Disordered proliferative endometrium can also show irregular glands; however this change is more focal than in hyperplasia. The basalis may show glandular crowding; however the glands should be inactive, not proliferative type.

3.3 Metaplastic Change

The endometrium can demonstrate different types of metaplastic change, including eosinophilic, ciliated, squamous, mucinous, and clear cell change. Metaplasia can occur in benign endometrium, hyperplasia, and carcinoma, which can obfuscate the underlying process. Eosinophilic change, for example, shows rounding of cells that can be mistaken for cytologic atypia. Squamous differentiation is fairly common and has traditionally been thought to manifest in morular or non-morular forms. In morular metaplasia, round nests of bland oval or spindled cells are seen that resemble squamous epithelium, hence the name "squamous" morules. Morular metaplasia has been proposed as an alternative name as the squamous nature of these cells has been questioned recently due to different staining patterns than non-morular squamous differentiation. Morular metaplasia expresses CDX2 (a marker often associated with gastrointestinal differentiation) and does not express p63 (a marker of squamous differentiation) while non-morular squamous differentiation demonstrates the opposite staining pattern. Morular metaplasia is often seen with hyperplasia, and its presence should raise suspicion for possible hyperplasia or carcinoma. Distinguishing atypical hyperplasia from adenocarcinoma is discussed in the Sect. 4.1.1.

3.4 Progestin Effect

Progestin is commonly used to treat atypical hyperplasia as well as some cases of well-differentiated endometrioid adenocarcinoma. The characteristic histologic feature of progestin treatment is pseudodecidualized stroma where the stromal cells become large, round, and plump, with abundant pink cytoplasm. The glands may be inactive or show eosinophilic change that should be distinguished from residual atypia.

4 Uterine Tumors

4.1 Endometrial Carcinoma

Endometrial carcinomas occur more often in postmenopausal women and usually present with abnormal vaginal bleeding. They can be divided into two types: type 1 and type 2. Type 1 tumors are associated with unopposed estrogen and are usually low grade. Endometrioid adenocarcinoma is the prototypical type 1 tumor. Type 2 tumors are not associated with unopposed estrogen, tend to be high grade, and occur more frequently in an older age group than those who develop type 1 tumors. Serous carcinoma is an example of a type 2 carcinoma. Different types of endometrial carcinoma will be discussed below.

4.1.1 Endometrioid Adenocarcinoma

Endometrioid adenocarcinomas comprise 60–80 % of endometrial carcinomas. Grossly, these tumors may be unifocal or multifocal and often present as an exophytic, friable mass (Fig. 3). However, in some cases, particularly in small, atrophic uteri, the tumor manifests primarily as thickened endometrium and myometrium and may be difficult to identify grossly. Identifying the tumor grossly is clinically significant since

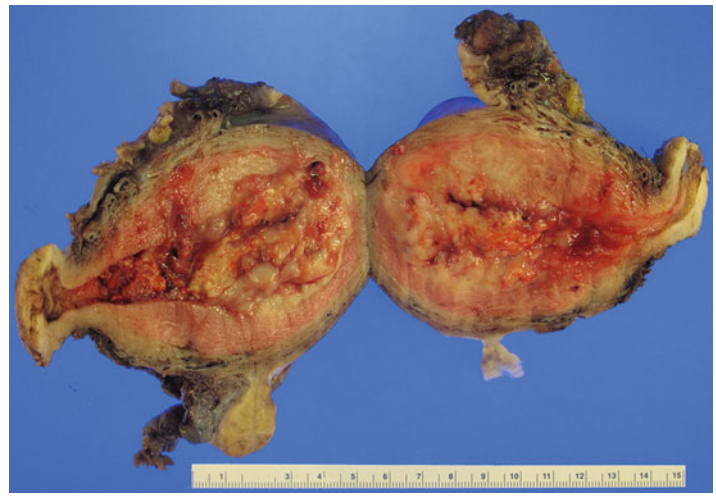

Fig. 3 Endometrioid adenocarcinoma. Gross photograph of a bivalved uterus showing a large, friable, tan-white mass filling the uterine cavity and invading into the myometrium

Table 1 Grading of endometrioid adenocarcinoma

	Architectural grade	Nuclear grade
Grade 1	Less than 5 % solid areas	Uniform, round to oval nuclei; inconspicuous nucleoli
Grade 2	5–50 % solid areas	Irregular nuclei with chromatin clumping
Grade 3	Greater than 50 % solid areas	Large, pleomorphic nuclei with prominent nucleoli

Overall grade is based on both architecture and nuclear grade. Tumor grade is increased by one if nuclear grade is discordant with architectural grade, e.g., a tumor should be upgraded from grade 1 to 2 if it has grade 1 architecture and grade 2 nuclei

intraoperative consultation is often performed for staging purposes and the pathologist must identify the point of deepest invasion (whether tumor involves more than half of the myometrium) which may not always be evident on gross examination.

Microscopically, endometrioid adenocarcinoma consists of proliferative type endometrium with pseudostratified columnar cells showing crowded glands with complex architectural patterns and cytologic atypia. The extent of architectural and cytologic atypia should be greater than that seen in atypical hyperplasia/EIN. Differentiating between these two entities is further discussed below. The presence of invasive glands in the myometrium is pathognomonic for adenocarcinoma.

Endometrioid adenocarcinoma is graded using the International Federation of Gynecology and Obstetrics (FIGO) grading system. The tumor is divided into three grades based on both architecture and nuclear atypia. Architectural grade is based on the degree of gland formation: grade 1 = solid areas comprise less than 5 % of the tumor, grade 2 = solid areas comprise 5–50 % of the tumor, and grade 3 = solid areas comprise more than 50 % of the tumor (Table 1) (Figs. 4 and 5). Nuclear grade is defined as follows: nuclear grade 1 = uniform round and oval nuclei, nuclear grade 2 = irregular nuclei with chromatin clumping, and nuclear grade 3 = large, pleomorphic nuclei that may show prominent nucleoli.

The nuclear grade of the tumor is usually consistent with the architectural features, e.g., endometrioid adenocarcinoma with low-grade architecture usually has low-grade nuclei. Under the FIGO grading system, if a tumor with grade 1 architecture shows grade 2 nuclei, the tumor should be upgraded to an overall grade 2 tumor. Caution should be used in upgrading though as the presence of marked architectural/nuclear

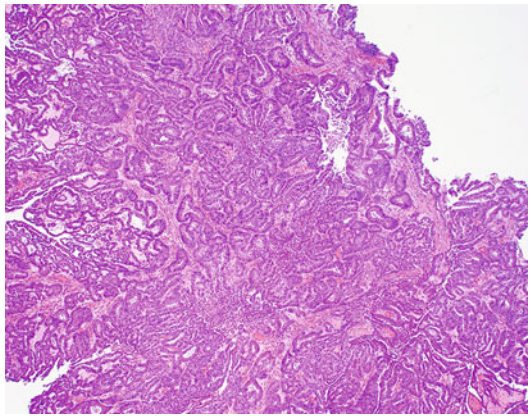

Fig. 4 Endometrioid adenocarcinoma, grade 1. The tumor is composed entirely of glands that are back to back and confluent with cytologic atypia

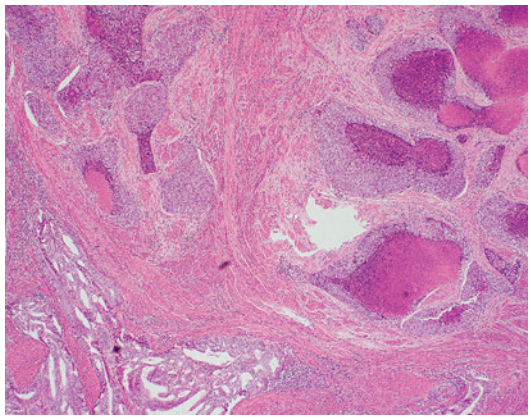

Fig. 5 Endometrioid adenocarcinoma, grade 3. The tumor shows predominantly solid nests of cells with central necrosis, invading the myometrium. In the lower left corner, gland formation is seen

atypia dyssynchrony should raise suspicion that the tumor is actually serous carcinoma rather than endometrioid type as serous carcinomas show high-grade nuclei with gland formation. When evaluating tumor architecture, areas of squamous differentiation should not be included as solid areas.

4.1.2 Villoglandular and Secretory Carcinoma

Several variants of endometrioid adenocarcinoma exist. Two distinctive ones that can mimic serous and clear cell carcinomas are villoglandular and secretory carcinomas, respectively.

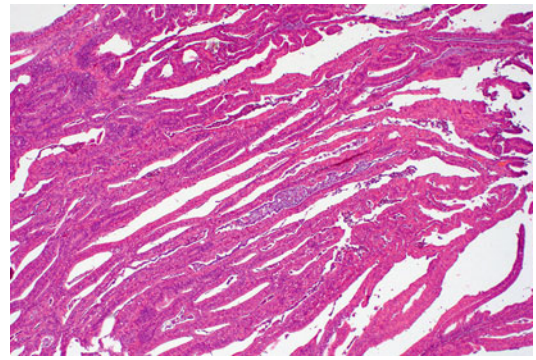

Fig. 6 Villoglandular carcinoma. The tumor shows long, villous papillae with low-grade nuclei

Villoglandular carcinomas are characterized by long, villous papillae with fibrovascular cores and bland, columnar cells (Fig. 6). The percentage of the tumor that should show villoglandular features in order to be classified as villoglandular carcinoma is not well-defined, but should be at least the majority of the tumor. Villoglandular carcinomas can resemble serous carcinomas due to papillary architecture; however marked nuclear atypia is not typical in villoglandular carcinomas as it is in serous carcinomas. The prognosis of villoglandular carcinomas is based primarily on grade and stage as in other endometrioid adenocarcinomas and because these tumors are primarily low grade, they tend to have a good prognosis.

Secretory adenocarcinoma is rare and defined by the presence of cytoplasmic vacuoles as seen in secretory phase glands. It is a low-grade tumor with bland, uniform cells and is associated with a good prognosis. Secretory carcinoma is further discussed under clear cell carcinoma, a tumor it can mimic.

Other subtypes of endometrioid adenocarcinoma can show metaplastic change such as ciliated and clear cell change. The significance of recognizing variant features is to not misdiagnose endometrioid adenocarcinoma as a different tumor such as clear cell carcinoma. Mentioning such features also helps to identify the tumor on an excisional specimen or recurrence. Metaplastic

change in endometrioid adenocarcinoma is not prognostically significant.

4.1.3 Commonly Encountered Problems in Pathologic Diagnosis and Staging of Endometrioid Adenocarcinoma

Several areas in diagnosis and staging of endometrioid adenocarcinoma can be problematic, with some issues more frequently encountered than others. The issues are enumerated below:

1. Endometrioid adenocarcinoma versus atypical hyperplasia/EIN

   The line between atypical hyperplasia and adenocarcinoma can be blurry, and the diagnosis is subject to interobserver variability. Confluent glands, back-to-back glands with little to no intervening stroma, increased architectural complexity such as cribriforming or papillary architecture in more than a minute focus, greater nuclear atypia than that seen in atypical hyperplasia, and the presence of desmoplasia favor a diagnosis of adenocarcinoma. Desmoplasia however is rarely seen in endometrioid adenocarcinoma. In endometrial biopsy specimens, a diagnosis of "atypical hyperplasia bordering on low-grade endometrioid adenocarcinoma" may be appropriate in certain cases with the final diagnosis deferred to the excisional specimen.
2. Myometrial invasion

   Myometrial invasion is measured from the endomyometrial junction to the deepest point of invasion. Several issues must be considered in determining both the presence of myometrial invasion and depth of invasion.

   (a) The endomyometrial junction is irregular making it difficult to assess for invasion. Superficial myometrial invasion tends to be overdiagnosed. Clues to invasion are jagged, angular glands and desmoplasia. The diagnosis of superficial invasion can be highly subjective as borne out by data showing no difference in prognosis between those with tumors confined to the endometrium and those with tumors involving the upper half of the myometrium. Based on this evidence, in 2009, FIGO changed the staging system so tumors confined to the endometrium and involving the upper half of the myometrium are both now staged as Ia.

   (b) Myometrial invasion can manifest as glands infiltrating the myometrium or as a pushing border. In cases of a pushing border, without the presence of normal endomyometrial junction for comparison, it can be difficult to diagnose invasion.

   (c) Myometrial invasion should not be diagnosed when malignant glands involve adenomyosis. Adenomyosis is when benign endometrial tissue, both glands and stroma, are found in the myometrium. Adenocarcinoma involving adenomyosis is not true myometrial invasion. The rounded contour of adenomyosis versus the angulated glands of true invasion, the presence of benign glands adjacent to malignant glands, areas of uninvolved adenomyosis elsewhere, and the presence of endometrial stroma in adenomyosis favor a diagnosis of tumor involving adenomyosis. In some tumors, there can be both tumor involving adenomyosis and true myometrial invasion.

   (d) An unusual type of invasion, microcystic, elongated, and fragmented (MELF) invasion, has been described. In this type of invasion, glands are surrounded by inflamed fibromyxoid stroma that can almost obscure the glands. The glands themselves may be flat and resemble lymphovascular spaces. The significance of MELF however is still controversial.

4.1.4 Serous Carcinoma

Serous carcinomas of the uterus are aggressive tumors that have a propensity to spread to peritoneal surfaces and commonly present at a late stage. They comprise 5–10 % of endometrial cancers and are usually found in women over 65. Serous carcinomas of the uterus are by definition high grade. They can be found in pure form,

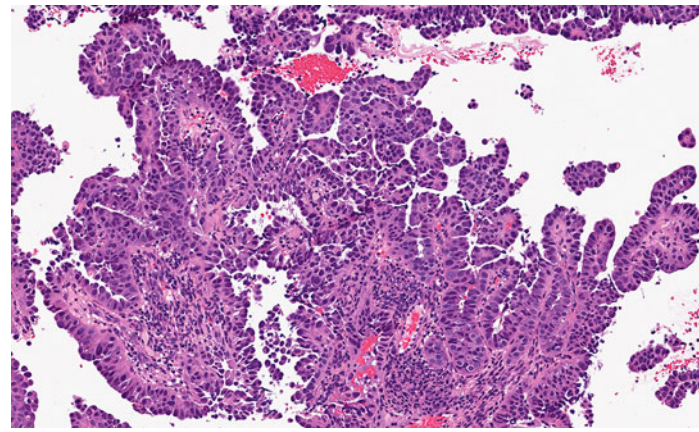

Fig. 7 Serous carcinoma. Papillary architecture is seen with markedly atypical nuclei and detached cells

admixed with other high-grade carcinomas such as high-grade endometrioid carcinoma or clear cell carcinoma, or found as a component of MMMT.

Grossly, serous carcinomas usually present as a friable, exophytic mass. Microscopically, serous carcinomas classically exhibit papillary or micropapillary architecture with fibrovascular cores; small glands and solid areas can also be seen. The cells often show tufting into the lumen and exfoliated cells are present. Cytologically, the cells are round to cuboidal, with large, pleomorphic, often vesicular nuclei and prominent nucleoli (Fig. 7). Brisk mitotic activity is common and hobnailing is not infrequent. Psammoma bodies are another feature classically associated with serous carcinomas.

The differential diagnosis of serous carcinoma includes clear cell carcinoma, MMMT, villoglandular carcinoma, high-grade endometrioid carcinomas, and eosinophilic syncytial change. Distinguishing serous carcinoma from some of these other lesions is discussed in the pertinent sections of the aforementioned lesions. Serous carcinomas tend to be either diffusely positive or completely negative or "null" for p53 and diffusely positive for p16 while endometrioid carcinomas show heterogeneous staining with p53 and p16. The combination of morphology and pattern of immunostaining should help to distinguish serous carcinoma from its mimics. Eosinophilic syncytial change, also referred to as eosinophilic syncytial metaplasia, is seen in association with endometrial breakdown. The epithelial cells are eosinophilic and can show enlarged nuclei with pseudopapillary architecture that can mimic serous carcinoma. The background of breakdown and minimal pleomorphism should help to distinguish this change from malignancy.

Another problem that can be encountered with serous carcinomas is determining the primary site. When there is widespread tumor involving the uterus, ovaries, and fallopian tubes, a fallopian tube primary would be favored. Synchronous primaries should also be considered. The absence of uterine serosal involvement would be more consistent with a uterine primary.

The precursor to serous carcinoma is serous endometrial intraepithelial carcinoma (EIC). Serous EIC involves only the surface epithelium, showing markedly atypical cells lining the epithelium. An intraepithelial or in situ lesion should by definition have no capacity to metastasize as it has not yet invaded the stroma. In other tumors, such is the case but serous EIC behaves differently than other in situ lesions, demonstrating a propensity to spread just like invasive serous carcinoma (Sherman et al. 1992). Serous carcinoma confined to endometrial polyps also demonstrates aggressive behavior (Silva and Jenkins 1990).

4.1.5 Clear Cell Carcinoma

Clear cell carcinomas are high-grade, aggressive tumors that comprise less than approximately 5 % of uterine malignancies. They tend to occur in

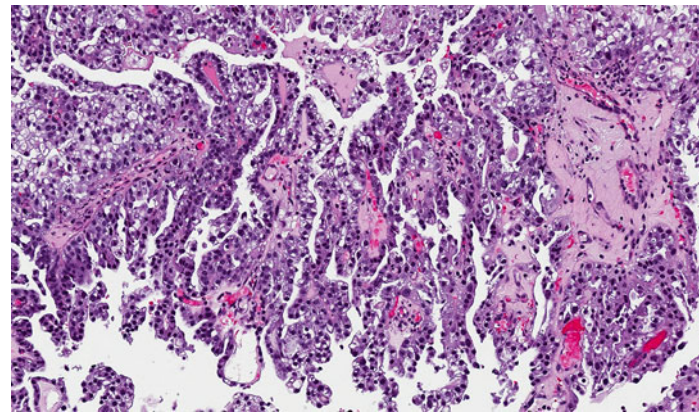

Fig. 8 Clear cell carcinoma. Papillary architecture is seen with clear cells and stromal hyalinization

women older than 65 and, like serous carcinoma, are high-grade tumors by definition (Abeler and Kjorstad 1991).

Grossly, clear cell carcinoma presents as a uterine mass without any distinctive features. Microscopically, the tumor shows papillary, tubulocystic, and solid architecture, usually exhibiting a mixture of patterns. Per its name, cells with clear cytoplasm due to glycogen are often seen (Fig. 8). Another characteristic feature is hobnail cells. Hobnail refers to a cell with bulbous nuclear protrusion and a narrow base; hobnail is literally a short nail with a wide head. The hobnail cells may have either clear or eosinophilic cytoplasm. The cells show high-grade features such as pleomorphism and large nuclei with prominent nucleoli. Hyalinized stroma and hyaline bodies (homogeneous eosinophilic droplets) are also commonly seen.

Clear cells are not pathognomonic for clear cell carcinoma as clear cells can be encountered in a variety of lesions, both benign and malignant. Clear cell carcinomas should be distinguished from Arias-Stella reaction, secretory carcinoma, endometrioid carcinoma with clear cell change, and serous carcinoma.

Arias-Stella reaction is a benign change that usually occurs during pregnancy. It is characterized by atypical clear and hobnail cells mimicking malignancy. Features of Arias-Stella reaction that help to distinguish it from clear cell carcinoma include the following: it occurs in premenopausal women, does not show invasion, shows little to no mitotic activity, and is an incidental finding. Secretory carcinoma may show solid areas with clear cells that resemble clear cell carcinoma. The low-grade cytology of secretory carcinoma should help to distinguish it from the marked nuclear atypia seen in clear cell carcinoma. Serous carcinomas exhibit high-grade nuclei just as in clear cell carcinomas; however presence of extensive clearing or other features associated with clear cell carcinoma such as hyalinization would favor clear cell carcinoma. Endometrioid carcinoma with clear cell change is not likely to show marked nuclear atypia.

Immunostains have limited utility in the diagnosis of clear cell carcinomas, as these tumors do not show a specific pattern of immunostaining. However, it can help in some instances. Clear cell carcinomas tend to be estrogen receptor/progesterone receptor (ER/PR) negative versus endometrioid adenocarcinomas that are clear cell carcinomas also tend to show heterogeneous expression of p53 which may help to differentiate them from serous carcinomas that tend to be diffusely positive or completely null for p53.

4.1.6 Undifferentiated Carcinoma

Undifferentiated carcinomas are rare tumors that, despite their name, have distinctive histologic features and should not be used as a wastebasket diagnosis for tumors that cannot be classified (Altrabulsi et al. 2005). Microscopically, these tumors are characterized by sheets of monotonous, epithelioid, medium-sized cells with cytokeratin expression in usually less than 10 % of cells. Prominent nucleoli, vesicular

nuclei, brisk mitoses, and necrosis are usually seen. A marked lymphoid infiltrate may also be present.

The differential diagnosis includes grade 3 endometrioid carcinoma, endometrial stromal sarcoma, high-grade sarcoma, neuroendocrine carcinoma, and lymphoma. Immunostains can help to differentiate between these entities: cytokeratin will show greater expression in pure endometrioid carcinomas, endometrial stromal sarcoma tends to be CD10 positive, high-grade sarcoma should show a pattern of immunostaining consistent with the differentiation seen, and lymphoma tends to be CD45 positive. Synaptophysin and chromogranin are markers of neuroendocrine differentiation that can be focally (usually less than 10 %) expressed in undifferentiated carcinomas (Taraif et al. 2009) while neuroendocrine carcinomas should show greater expression of these two markers and also show neuroendocrine histology. Undifferentiated carcinomas are aggressive tumors with a poor prognosis.

4.1.7 Mixed-Type Carcinoma

Mixed carcinomas refer to tumors showing carcinomas of at least two different types. The most commonly encountered mixed carcinomas are endometrioid adenocarcinoma with serous carcinoma, endometrioid adenocarcinoma with clear cell carcinoma, and endometrioid adenocarcinoma with undifferentiated carcinoma. Endometrioid adenocarcinoma and its variants, such as secretory carcinoma, are not considered mixed carcinomas. When endometrioid adenocarcinoma is seen with variant features, it should be diagnosed as endometrioid adenocarcinoma with clear cell features, for example, rather than a mixed tumor. The percentage of each histologic type should be stated in mixed carcinomas as this can have prognostic value.

4.1.8 Lynch Syndrome

Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant disorder with incomplete penetrance that increases the risk of various cancers, particularly colorectal and endometrial cancer. The lifetime risk for endometrial cancer has been found to be as high as 60 % in Lynch syndrome. Endometrial cancers in Lynch syndrome demonstrate microsatellite instability (MSI) which is excessive repetition of short DNA sequences secondary to a defective DNA repair system. Twenty-five to 30 % of sporadic endometrial tumors also exhibit MSI. Both endometrioid and non-endometrioid carcinomas can show MSI. Screening guidelines for Lynch syndrome are not standardized, but some groups recommend routine screening in women under the age of 50 who are diagnosed with endometrial carcinoma. Screening for MSI in Lynch-associated endometrial carcinomas can be performed with a panel of immunostains for the mismatch repair proteins, MLH1, MSH2, MSH6, and PMS2. Loss of expression in one or more of these stains suggests MSI and further genetic testing is then indicated.

4.2 Mesenchymal Lesions

4.2.1 Endometrial Stromal Tumors

Endometrial Stromal Nodule

Endometrial stromal nodules are the benign counterpart of endometrial stromal sarcomas. They are composed of small round to ovoid blue cells as seen in endometrial stromal sarcoma but are confined to the endometrium without myometrial involvement while endometrial stromal sarcoma involves the myometrium.

Endometrial Stromal Sarcoma

Endometrial stromal sarcomas were traditionally divided into low- and high-grade types. In 2003, WHO classified these tumors into two groups, endometrial stromal sarcoma, with no designation of low or high grade, and undifferentiated endometrial sarcoma. In the most recent WHO, these group of tumors are divided into low-grade and high-grade endometrial stromal sarcoma and undifferentiated endometrial sarcoma based on recent evidence showing a common translocation in the tumors now designated high-grade endometrial stromal sarcoma (Kurman et al. 2014).

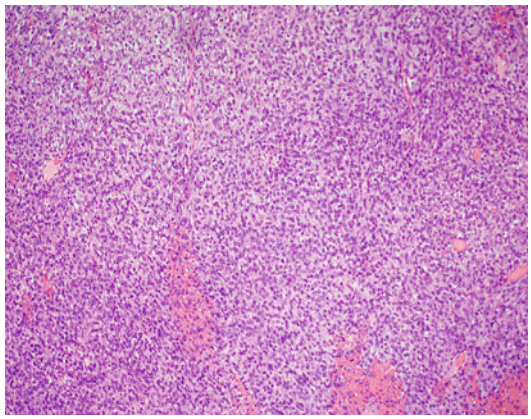

Fig. 9 Endometrial stromal sarcoma. Sheets of monotonous, small, round blue cells are seen

Low-Grade Endometrial Stromal Sarcoma

Low-grade endometrial stromal sarcomas are low-grade malignant tumors that tend to occur in premenopausal women (median age 40). Women present with abnormal vaginal bleeding or abdominal pain.

Grossly, endometrial stromal sarcoma is classically described as showing a "wormlike" appearance that is primarily due to nodules of tumor in vascular spaces. It can also manifest as a solid mass with diffuse involvement of the myometrium.

Microscopically, the tumor consists of highly cellular, monotonous, small round to ovoid blue cells that forms large irregular nests and invades the myometrium as irregular tongues (Fig. 9); spindle cell forms can also be seen. Mitotic activity is usually low. A classic feature of endometrial stromal sarcoma is the presence of numerous small vessels resembling endometrial spiral arterioles. Vascular invasion is common. Endometrial stromal sarcoma can exhibit different elements, including smooth muscle differentiation, sex cord-like elements, and gland formation.

CD10 is the immunostain typically associated with endometrial stromal sarcoma; however it is not very specific. Endometrial stromal sarcomas also tend to express ER and PR. In the majority of typical endometrial stromal sarcomas, JAZF1-SUZ12 fusion is present secondary to t(7;17)(p15;q21) (Kurman et al. 2014).

The differential diagnosis of endometrial stromal sarcoma includes endometrial stromal nodule, smooth muscle lesions, adenomyosis, and adenosarcoma. As stated previously, the main difference between endometrial stromal sarcoma and endometrial stromal nodule is the presence of myoinvasion. In an endometrial biopsy, distinguishing between the two may be impossible, but endometrial stromal sarcoma would be more likely. In some cases, it can be difficult to distinguish endometrial stromal sarcoma from smooth muscle tumors, particularly cellular leiomyoma and intravenous leiomyomatosis. Since both endometrial stromal sarcomas and smooth muscle tumors can express CD10 and smooth muscle markers, a panel of immunostains, rather than one or two immunostains, is recommended to differentiate between the two (see IHC chapter). Adenomyosis can be gland-poor such that only nests of endometrial stroma are seen in the myometrium that can raise suspicion for endometrial stromal sarcoma. Unlike endometrial stromal sarcoma, however, a mass should not be apparent, the stromal cells may appear atrophic, and adenomyosis with sparse glands is more likely to occur in postmenopausal women while endometrial stromal sarcoma is more common in premenopausal women. Adenosarcoma is discussed below.

High-Grade Endometrial Stromal Sarcoma

Recently, a specific genetic alteration was identified in a subset of tumors that are now designated as high-grade endometrial stromal sarcoma by WHO. High-grade endometrial stromal sarcoma exhibits a specific translocation, t(10;17)(q22;p13), which causes YWHAE-FAM22 fusion (Lee et al. 2012). Microscopically, the tumor consists of large, round cells with frequent mitoses and necrosis. Bland spindled cells may also be present. CD10 is negative in the high-grade round cells but tends to be expressed by the low-grade spindled cells. Cyclin D1 staining has also been found in these tumors.

Undifferentiated Endometrial Sarcoma

Undifferentiated endometrial sarcomas are aggressive, high-grade sarcomas. They are rare,

occur primarily in postmenopausal women, and present with either abnormal vaginal bleeding or systemic symptoms related to late stage disease.

Microscopically, sheets of pleomorphic oval or spindled cells are seen, usually with necrosis and brisk mitoses. The tumor tends to replace the myometrium, rather than infiltrating it as endometrial stromal sarcoma does. The immunoprofile of undifferentiated endometrial sarcomas is not specific. Undifferentiated endometrial sarcoma may express CD10 and ER like endometrial stromal sarcoma but exhibits much weaker expression. Due to the fairly nonspecific histology of this tumor, the differential is broad, including other high-grade tumors such as high-grade leiomyosarcoma, sarcomatous component of MMMT, and undifferentiated endometrial carcinoma. Undifferentiated endometrial sarcoma is therefore a diagnosis of exclusion after ruling out other lesions.

4.2.2 Smooth Muscle Tumors

Leiomyoma

Leiomyomas are not only the most common tumor in the uterus; uterine leiomyomas are the most common neoplasm in humans. Grossly, classic features of uterine leiomyomas are circumscribed, tan-white solid masses with a whorled appearance on cut surface. Microscopically, leiomyomas show fascicles of uniform cigar-shaped spindle cells with little to no nuclear atypia, low to moderate cellularity, and little to no mitotic activity.

Leiomyosarcoma

Leiomyosarcomas are rare, aggressive tumors that are the most common pure mesenchymal malignancy of the uterus. It is most common in women in their 50s. Diagnosing a leiomyosarcoma requires recognition of two elements: (1) smooth muscle differentiation and (2) that it is malignant. Clinically, leiomyosarcoma may be suspected versus a leiomyoma when there is a single large mass versus multiple masses (leiomyomas) or a dominant large mass among multiple masses.

Grossly, leiomyosarcomas are usually large (10 cm or greater) and have a fleshy variegated appearance with infiltrative margins and necrosis. Microscopically, conventional leiomyosarcomas consist of fascicles of spindled cells with high cellularity, nuclear atypia, and brisk mitoses. Tumor cell necrosis may or may not be seen. The criteria for malignancy in smooth muscle tumors are moderate to marked nuclear atypia, mitotic rate $\geq$10 mitoses/10 HPF, and tumor cell necrosis. Leiomyosarcoma should be diagnosed when two of the three criteria are met.

Distinguishing between tumor cell necrosis and infarct-type necrosis is a well-known problematic issue in uterine smooth muscle neoplasms. Tumor cell necrosis is a criterion of malignancy while infarct-type necrosis is not. Infarct-type necrosis can be seen in leiomyomas but tumor cell necrosis should not be present, while one or both types of necrosis may be present in leiomyosarcomas, but only tumor cell necrosis qualifies as a criterion of malignancy. Tumor cell necrosis shows abrupt transition from necrotic cells to viable tumor while infarct-type necrosis shows granulation tissue or fibrosis between necrosis and viable cells. Sometimes, the type of necrosis present is indeterminate and such cases, in combination with other features, may best be classified as smooth muscle tumors of unknown malignant potential (STUMP). Another confounding factor is that treated leiomyomas can be necrotic. Another criterion of malignancy, mitotic count, is also not always straightforward. Mitotic count can be overestimated if some cells showing nuclear condensation or smudging that can resemble mitotic figures are counted.

Two variants of leiomyosarcoma are epithelioid and myxoid types. The criteria for malignancy in these variants are somewhat different from conventional type, with both variants only requiring $\geq$5 mitoses/10 HPF rather than $\geq$10 mitoses/10 HPF. Epithelioid leiomyosarcomas have epithelioid or round cells, rather than spindled cells, that demonstrate smooth muscle differentiation by immunohistochemistry. Myxoid leiomyosarcomas, as their name states, show diffuse myxoid change and can have a deceptively bland appearance with low cellularity that may be construed as a benign lesion.

Smooth muscle differentiation can be confirmed with various smooth muscle markers if

necessary. The most commonly used immunostains are smooth muscle actin (SMA), desmin, and h-caldesmon. In addition, ER/PR expression may be seen.

Several variants of leiomyomas are recognized that can be mistaken for leiomyosarcomas. They include cellular leiomyoma, leiomyoma with bizarre cells, mitotically active leiomyoma, among others. Cellular leiomyomas, per their name, show high cellularity. Mitotically active leiomyomas can have greater than 10 mitoses/10 HPF but should not show atypical mitoses. Leiomyomas with bizarre cells have also been referred to as symplastic leiomyomas or atypical leiomyomas and show scattered markedly atypical or bizarre cells that can show multinucleation. The aforementioned variants demonstrate a feature that is suspicious for malignancy or a criterion for malignancy; however, they do not have other criteria for malignancy.

The differential diagnosis of leiomyosarcoma depends on its type. Spindled or conventional leiomyosarcomas should be differentiated from cellular leiomyomas, MMMT, endometrial stromal sarcoma, spindle cell rhabdomyosarcoma, undifferentiated sarcoma, and other sarcomas. The differential diagnosis of epithelioid leiomyosarcoma is broad and includes carcinomas, PEComa, malignant melanoma, and other sarcomas. The differential diagnosis of myxoid leiomyosarcoma includes myxoid leiomyoma, myxoid variant of endometrial stromal sarcoma, and myxoid change within the myometrium. Careful attention to histologic features, immunostaining, and clinical information can help in differentiating between the different entities.

Smooth Muscle Tumor of Unknown Malignant Potential

Smooth muscle tumors with equivocal features between leiomyoma and leiomyosarcoma are best classified as smooth muscle tumor of unknown malignant potential or STUMP. Some have also referred to these lesions as atypical smooth muscle tumors, a designation that can be confusing as the term atypical leiomyoma has also been applied to a different lesion, leiomyoma with bizarre cells. STUMP shows some criterion for malignancy that is insufficient to render an unequivocal diagnosis of malignancy. An example would be a lesion with moderate nuclear atypia but no tumor cell necrosis and less than 10 mitoses/10 HPF.

4.3 Mixed Epithelial-Mesenchymal Tumors

4.3.1 Adenosarcoma

Adenosarcoma is a malignant biphasic tumor with a malignant mesenchymal component (sarcoma) and benign epithelial component. It can occur in all ages and usually presents with abnormal vaginal bleeding. Grossly, a polypoid mass is usually seen. Microscopically, adenosarcoma is morphologically similar to phyllodes tumor of the breast and classically shows broad polypoid fronds. The tumor consists of malignant spindled cells and dilated glands of varying shape lined by proliferative type endometrium. The sarcomatous component most often resembles endometrial stromal sarcoma but can exhibit heterologous differentiation. The mesenchymal component should show nuclear atypia, $\geq$2 mitoses/10 HPF, and periglandular cuffing. Periglandular cuffing refers to increased cellularity or condensation of cells around glands and is a distinctive feature of adenosarcomas. The epithelium can show metaplasia such as squamous and ciliated change and may exhibit some cytologic atypia but is not frankly malignant.

The differential diagnosis includes adenofibroma, adenomyoma, MMMT, and sarcomas. Adenofibroma is the benign counterpart of adenosarcoma. Adenomyoma is another polypoid lesion consisting of benign glands with benign stroma with a predominant smooth muscle component. Lack of malignant features of the mesenchymal component should help to identify both adenofibromas and adenomyomas. MMMT will show malignant epithelium, unlike adenosarcomas. A biopsy of an adenosarcoma may mimic pure sarcoma if the epithelial component is not evident; in some cases, diagnosis is best made on the excisional specimen.

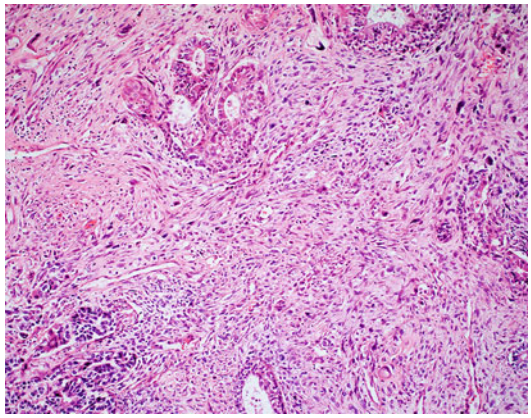

Fig. 10 Malignant mixed Mullerian tumor (MMMT). Biphasic pattern with glands and pleomorphic spindle cells is seen

Immunostains are usually not necessary for diagnosis; if performed, the sarcomatous component will usually stain like endometrial stromal sarcomas, expressing CD10, ER, PR, and WT1.

Adenosarcomas may recur in 25 % of cases. Cases with sarcomatous overgrowth (≥25 % high-grade sarcomatous component) tend to be more aggressive (Clement 1989).

4.3.2 Malignant Mixed Mullerian Tumor

Malignant mixed Mullerian tumor (MMMT) or carcinosarcoma is a biphasic tumor with both epithelial and mesenchymal elements. They comprise less than 5 % of uterine malignancies and occur almost exclusively in postmenopausal women.

Grossly, MMMT may present as a polypoid mass and exhibit a fleshy appearance. Microscopically, the presence of malignant glands admixed with high-grade spindled cells is essentially diagnostic of MMMT (Fig. 10). These tumors however can exhibit varying histology. The epithelial component may show elements of endometrioid, serous, or other high-grade carcinomas, including unclassifiable carcinoma, while the mesenchymal component can be homologous and/or heterologous. Homologous elements refer to finding cells showing differentiation indigenous to the uterus, such as smooth muscle, while heterologous elements refer to the presence of tissue not usually found in the uterus, such as skeletal muscle. The homologous component in MMMT is often high-grade spindled or pleomorphic cells, while the heterologous component is often rhabdomyosarcoma (skeletal muscle differentiation) or chondrosarcoma (cartilaginous differentiation). The proportion of the epithelial to the mesenchymal component can vary. In some cases, the epithelial component may so predominate in an endometrial biopsy that MMMT can only be diagnosed on the excision. Lymphovascular invasion is common.

In MMMT, cytokeratin immunostains are not only expressed by the epithelial component but also tend to stain the mesenchymal component. The differentiation of the mesenchymal component can be demonstrated if necessary with stains such as desmin and myogenin for rhabdomyosarcoma but is usually not necessary.

The differential diagnosis of MMMT includes endometrioid carcinoma with spindle cells, endometrioid adenocarcinoma with heterologous elements, mixed endometrioid and undifferentiated carcinoma, and adenosarcoma. Endometrioid carcinoma with spindle cells should not show immunostaining for a mesenchymal component, heterologous elements in endometrioid adenocarcinoma should not be malignant as they are in MMMT, mixed endometrioid and undifferentiated carcinoma will usually show a low-grade epithelial component compared with the high-grade epithelial component seen in MMMT, and in adenosarcoma, the epithelial component is benign.

MMMT are aggressive tumors with a poor prognosis. Heterologous tumors had been thought to have a poorer prognosis at one time; however that is currently controversial. When MMMT metastasize, the epithelial component is more likely to be seen.

4.4 Other Uterine Tumors

4.4.1 Perivascular Epithelioid Cell Tumor

Perivascular epithelioid cell tumors (PEComas) are rare tumors of unclear origin that express

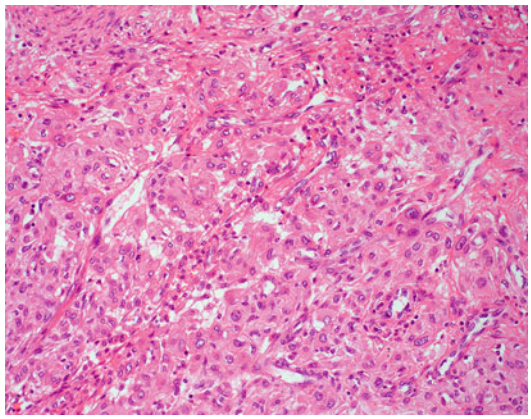

Fig. 11 Perivascular epithelioid cell tumor (PEComa). Nests of eosinophilic, epithelioid cells with mild pleomorphism are seen

both melanocytic (HMB-45, Melan-A) and smooth muscle markers (SMA, desmin). In some cases, PEComas are associated with tuberous sclerosis and lymphangioleiomyomatosis (LAM). Microscopically, fairly uniform, epithelioid or spindled cells with clear and eosinophilic cytoplasm are seen that classically show a nested growth pattern (Fig. 11). A prominent capillary pattern is usually present. Uterine PEComas may behave in a benign or malignant manner. One system proposed the following criteria for malignancy: size greater than 5 cm, high-grade nuclear atypia, necrosis, vascular invasion, $\geq$1 mitosis/50 HPF, and infiltrative growth pattern (Folpe et al. 2005). The differential diagnosis includes smooth muscle tumors, secondary involvement by gastrointestinal stromal tumors, malignant melanoma, and alveolar soft part sarcoma. Immunostains can help in diagnosis although smooth muscle neoplasms can also show expression of HMB-45 which can be a pitfall in diagnosis.

4.4.2 Primitive Neuroectodermal Tumor

Primitive neuroectodermal tumor (PNET) is an aggressive small round blue cell tumor thought to be of neuroectodermal origin that rarely occurs in the uterus. PNET is also referred to as Ewing sarcoma. Microscopically, sheets of monotonous, small, round cells are seen with brisk mitoses. A feature classically associated with PNET is rosettes; however they are not that commonly seen. Like PNET at other sites, uterine PNET tends to show membranous CD99 staining and FLI1 staining. They may also express neuroendocrine markers (synaptophysin, chromogranin). A characteristic translocation of these tumors is t(11;22) that leads to the fusion of EWS and FLI-1 genes. The differential diagnosis includes other round blue cell tumors such as small cell carcinoma, lymphoma, rhabdomyosarcoma, and endometrial stromal sarcoma.

4.4.3 Lymphoma

Non-Hodgkin lymphoma rarely involves the gynecologic tract. The female genital tract is the primary site of extranodal lymphomas in less than 2 % of cases (Cohn et al. 2007). Secondary involvement is more common. Most cases are diffuse large B-cell lymphoma. Patients may be asymptomatic or present with abnormal vaginal bleeding or nonspecific complaints such as bloating. Lymphoma is a round blue cell tumor that shows a diffuse growth pattern. It tends to expand the endometrium and grows around the endometrial glands. The differential diagnosis includes other round blue cell tumors such as undifferentiated carcinoma, neuroendocrine carcinoma, particularly small cell carcinoma, PNET, and endometrial stromal sarcoma. Benign processes such as reactive lymphoid infiltrates and chronic endometritis should also be considered. Ancillary testing with immunohistochemical staining is necessary for a correct diagnosis; flow cytometry would also be helpful.

5 Gestational Trophoblastic Disease

Gestational trophoblastic diseases are diseases that occur related to pregnancy. Some understanding of normal placental histology is necessary to understand gestational trophoblastic diseases. The placenta is composed of amnion and chorionic villi. Chorionic villi consist of a core of stroma

and capillaries lined circumferentially by cytotrophoblasts and syncytiotrophoblasts. Cytotrophoblasts are mononuclear, epithelioid cells with clear to eosinophilic cytoplasm. Syncytiotrophoblasts are multinucleated cells with hyperchromatic, smudgy nuclei. Intermediate or extravillous trophoblasts are another type of cell that helps anchor the placenta to the uterus and is usually found in the decidua. They can be epithelioid or spindled, have eosinophilic or amphophilic cytoplasm, and are usually mononuclear but can show multinucleation. Intermediate trophoblasts are thought to give rise to several gestational diseases, including exaggerated placental site, placental site nodule, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).

5.1 Hydatidiform Mole

Hydatidiform moles are products of abnormal fertilization and consist of partial and complete moles. Grossly, moles have a characteristic appearance often described as a "bunch of grapes" that consist of clear to opaque, small, delicate vesicles.

5.1.1 Complete Mole

Most complete moles develop when a single sperm or two sperm fertilize an egg that has lost its DNA, i.e., empty egg; hence all chromosomes in complete moles are usually paternally derived. Most complete moles have no fetal tissue and consist entirely of enlarged edematous villi or hydropic villi with circumferential trophoblastic proliferation. Cisterns or cavities are a characteristic feature. The stroma shows the absence of nucleated red blood cells that are seen in normal villi.

5.1.2 Partial Mole

Partial moles develop when a viable egg is fertilized by two sperm or by one sperm that duplicates itself leading to a triploid karyotype (69XXY or 69XXX). Partial moles have some fetal tissue and consist of a mixture of enlarged and normal-sized villi. Cisterns and nucleated red blood cells may be present. Fibrotic villi may be seen. Trophoblastic hyperplasia occurs but is less prominent than in complete moles.

Complete and partial moles need to be differentiated from hydropic villi of non-molar abortion or hydropic abortus as molar pregnancy has significant clinical implications. If histology is equivocal, ancillary studies can help to confirm the diagnosis. A fairly simple and cost-effective next step is p57 immunostaining. p57 is a biomarker expressed only in the maternal genome as it is paternally imprinted. In complete moles, p57 should be absent in cytotrophoblasts and villous stromal cells while in partial moles and hydropic villi, p57 is expressed. In some cases, p57 immunostaining may be equivocal and in these cases, further testing may be required.

DNA ploidy analysis can also be performed to determine whether a triploid (partial mole or hydropic abortus) or diploid (complete mole or hydropic abortus) population is present. Flow cytometry and fluorescent in situ hybridization (FISH) are two common methods of analysis; however one major limitation of these tests is that they will not distinguish hydropic abortus from partial moles. Currently, the best method for differentiating between the three entities is molecular genotyping with polymerase chain reaction (PCR) which requires maternal endometrial tissue.

Sequelae of molar pregnancy include persistent gestational disease (retained molar tissue and invasive moles), recurrence, and malignant gestational disease. Persistent and invasive moles occur in 15–20 % of complete moles and less than 4 % of partial moles (Conran et al. 1993). Beta-hCG is followed to monitor for persistent gestational disease, and methotrexate is used for treatment. As medical treatment is highly effective, histologic diagnosis of invasive moles is infrequent. However, if seen, invasive moles will show villi invading the myometrium. Distant metastasis can occur with invasive moles.

5.2 Malignant Gestational Disease

Choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic

tumor (ETT) are all rare malignancies that are associated with previous gestation, particularly with molar pregnancy. Choriocarcinoma is more strongly associated with molar pregnancy than the other two tumors. Choriocarcinoma tends to occur months after pregnancy, while PSTT and ETT usually occur many years afterwards. Abnormal vaginal bleeding is commonly the presenting symptom. In cases of choriocarcinoma and PSTT, the tumor may have already metastasized at the time of presentation so the presenting symptoms will be related to metastasis. Beta-hCG is elevated in all three tumors; however it is much higher in choriocarcinoma than in PSTT and ETT.

5.2.1 Choriocarcinoma

Less than 3 % of molar pregnancies lead to choriocarcinoma while half of choriocarcinomas are related to molar pregnancy. Twenty-five percent follow intrauterine gestation and 25 % follow abortion or tubal pregnancy.

Grossly, choriocarcinoma presents as a markedly hemorrhagic mass with necrosis. Microscopically, a solid proliferation of cells consisting of three cell types, cytotrophoblasts, intermediate trophoblasts, and syncytiotrophoblasts, is seen. A "biphasic" pattern of cytotrophoblasts alternating with syncytiotrophoblasts is characteristic of this tumor. Both cytotrophoblasts and syncytiotrophoblasts show pleomorphism. In some cases, syncytiotrophoblasts may not be apparent and beta-hCG staining can be performed to identify their presence as syncytiotrophoblasts are necessary to render a diagnosis of choriocarcinoma. Hemorrhage is typical, necrosis is often seen, and villi are not present.

5.2.2 Placental Site Trophoblastic Tumor

Grossly, an ill-defined mass is seen deeply invading the myometrium. Microscopically, sheets of pleomorphic, mononuclear, epithelioid cells with clear, eosinophilic, or amphophilic cytoplasm are seen. The cells tend to split smooth muscle fibers of the myometrium. Nuclear grooves may be seen. Brisk mitoses are typical and necrosis and hemorrhage frequent. Sometimes, the neoplastic cells can show multinucleation that should not be mistaken for syncytiotrophoblasts.

5.2.3 Epithelioid Trophoblastic Tumor

Grossly, a well-circumscribed tumor that deeply invades the myometrium with hemorrhage and necrosis is seen. Microscopically, mononuclear epithelioid cells with abundant clear or eosinophilic cytoplasm are seen like in PSTT but are less pleomorphic than in PSTT. Multinucleated cells may be seen. Necrosis and lymphocytic infiltrate are often seen.

The differential diagnosis of both PSTT and ETT are placental site nodule, exaggerated placental site, choriocarcinoma, and squamous cell carcinoma. Placental site nodule is a benign lesion that can be found years after pregnancy as residue of gestation. It is most often an incidental finding. Small hyalinized nodules of intermediate trophoblasts with variable nuclear atypia and clear and eosinophilic cytoplasm are seen. Placental site nodule should not form a mass like PSTT and ETT, and it also should have low Ki67 (less than 10 %) compared with Ki67 greater than 10 % in PSTT and ETT. Exaggerated placental site can show similar morphology to these tumors but is usually found after recent gestation. It also should have Ki67 less than 1 % (Kurman et al. 2011). Beta-hCG staining can be used to differentiate choriocarcinoma from these two entities. To distinguish squamous cell carcinoma from PSTT and ETT, immunostains can be used to identify squamous cells of squamous cell carcinoma versus the trophoblasts of PSTT and ETT. Both PSTT and ETT can show recurrence and metastasis, however do not appear to be as aggressive as choriocarcinoma.

6 Conclusion

Various lesions, both benign and malignant, occur in the uterus. The most common are benign leiomyomas and malignant endometrial carcinomas while more rare entities include gestational trophoblastic diseases. The mainstay of pathologic diagnosis is morphology; however, ancillary

studies such as immunohistochemical staining can be instrumental in diagnosing a lesion. Advances in molecular pathology have led to the identification of certain mutations such as the recently identified translocation in tumors now designated high-grade endometrial stromal sarcomas; undoubtedly, more mutations will be discovered creating a larger role for molecular testing to better classify and possibly treat uterine tumors.

7 Cross-References

- Abnormal Vaginal Bleeding During the Early Reproductive Years
- Conservative Management of Endometrial Cancer
- Diagnosis and Management of Gestational Trophoblastic Disease
- Diagnosis and Management of Postmenopausal Bleeding
- Diagnosis and Management of the Cancer of the Uterus
- Endometrial Hyperplasia
- Management of Abnormal Bleeding in Late Reproductive Years

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Germ Cell Tumors of the Ovaries

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Contents

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Abstract

The basic classification of ovarian germ cell tumors has largely remained unchanged for several decades. Ovarian germ cell tumors develop from primordial germ and stem cells that differentiate into extraembryonal and somatic tissues. In most cases, benign and malignant ovarian germ cell tumors can be correctly diagnosed due to their characteristic morphologic profiles. Several immunohistochemical (IHC) markers are widely available and can significantly facilitate tumor typing of germ cell tumors, especially in high grade tumors or in atypical clinical scenarios. In this chapter, the clinicopathologic features of ovarian germ cell tumors will be reviewed, with emphasis on morphology and diagnostically useful IHC markers.

Keywords

Germ cell tumors • Mature teratoma • Immature teratoma • Struma ovarii • Dysgerminoma • Yolk sac tumor • Embryonal carcinoma • Choriocarcinoma

1 Introduction

Ovarian germ cell tumors (OGCTs) are derived from neoplastic transformation of the ovarian primordial germ and stem cells. These tumors are unique because they form imperfectly formed "normal" human body tissues (Nogales et al. 2014). Germ cell tumors (GCTs) can be classified into: (1) tumors with mature elements which include mature cystic teratoma (MCT), (2) tumors with immature elements exhibiting range of differentiation and include dysgerminoma, embryonal carcinoma (EC), choriocarcinoma (CC), yolk sac tumor (YST), and immature teratoma (IT), and (3) malignant transformations such as squamous cell carcinoma (SCC), carcinoid, malignant struma ovarii and other rare neoplasms arising in a preexisting mature teratoma (Table 1) (Prat et al. 2014). Most GCTs are benign with straightforward pathologic diagnosis. Only rarely these tumors present diagnostic issues especially when occur in unusual clinical scenarios. On the other hand, malignant ovarian germ cell tumors (MOGCTs) or malignant transformation in an existing MCT account for a small fraction of OGCTs (Nogales et al. 2014).

2 Epidemiology and Clinical Presentation

While OGCTs constitute 20–25 % of all ovarian neoplasms, only <3 % are malignant. The prevalence is significantly higher (15 %) in Asian and black populations as compared to Caucasian populations (5 %) (Low et al. 2012). Clinical information including patient age, elevated serum markers, and presentation are important to report to the pathologic laboratory when specimens are being submitted, as they constitute a component of the pathologic evaluation and assessment. For example, benign MCTs predominate in reproductive-age women, immature teratomas and malignant GCTs predominate at young age (below 20), and somatic malignant transformation, e.g., SCC is more common in postmenopausal women (Nogales et al. 2014).

Patients are either asymptomatic with the tumor discovered incidentally on clinical or radiologic examinations or present with abdominal pain and/or a palpable abdominal mass. The mass may grow rapidly in a fraction of cases (~10 %) resulting in acute abdominal pain due to capsular distention, ischemic necrosis, hemorrhage, rupture, or torsion (Nogales et al. 2014). MOGCT may present with metastases. Alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), beta human chorionic gonadotropin (β-hCG), and cancer antigen 125 (CA-125) titers are some serum tumor markers used mainly for follow-up after treatment (Prat et al. 2014).

3 Mature Teratoma

Ovarian teratomas differentiate to mature tissues derived from the three germ layers. On the other hand, monodermal teratomas such as struma ovarii differentiate to one germ layer. Mature

Table 1 World Health Organization (WHO) classification of ovarian germ cell tumors[a]

Mature teratoma
Immature teratoma
Monodermal teratoma
Struma ovarii
Carcinoid
Somatic tumors arising from dermoid cyst
Squamous cell carcinoma and others
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma
Choriocarcinoma

[a]Only the most commonly encountered tumors in practice are included (Prat et al. 2014)

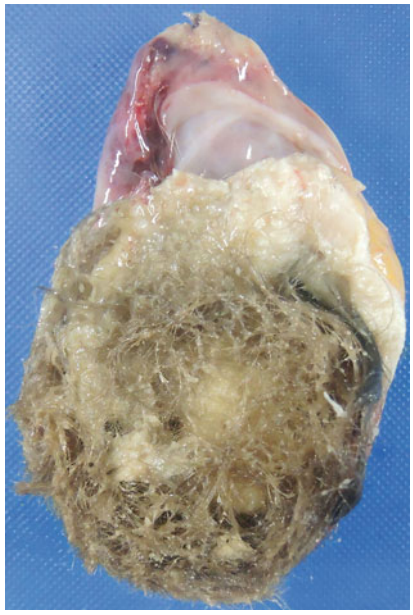

Fig. 1 Mature cystic teratoma containing hair tufts and sebaceous material

teratomas are the most common OGCTs accounting for ~20 % of all ovarian tumors, more than 90 % of OGCTs, and are the most common tumors seen in children (de Silva et al. 2004; Nogales et al. 2014).

3.1 Gross Pathology

Most lesions are mature cystic teratomas (MCTs). Approximately, 15 % of MCTs are bilateral. MCTs usually measure from 5 to 10 cm and contain a mixture of hair, skin, and malodorous sebaceous or keratinaceous material (Fig. 1). A raised protuberance (Rokitansky's tubercle) is often present and should be pathologically evaluated (Peterson et al. 1955). The cyst may be unilocular or multilocular, and the contents may appear hemorrhagic, similar to an endometriotic cyst. The more grossly complex the cyst is, the more likely the presence of other elements such as thyroid tissue (solid and brown mass).

3.2 Histopathology

Morphologically, MCTs are composed of various tissues derived from one or more germ layers. Ectodermal components, which are usually the most prominent, include skin with associated appendages (Fig. 2a) and mature neuroectodermal tissue (Fig. 2b), among others. Endodermal components include thyroid, salivary, and gastrointestinal tissues, among others (Fig. 2c, d). Mesodermal component includes muscle, cartilage (Fig. 2d), bone, and fat. MCTs may show minute neuroepithelial/ependymal areas which should not be reported as immature teratoma (Yanai-Inbar and Scully 1987). Gliomatosis peritonei (GP) is a teratoma associated with peritoneal nodules composed of mature glial tissue. Despite its advanced clinical stage (stage III), its behavior is benign if immature elements are absent. The origin for GP may be related to capsular rupture from the ovarian teratoma, although this is still largely speculative (Perrone et al. 1986; Peterson et al. 1955).

Ovarian mucinous tumors may be associated with mature cystic teratomas. These mucinous tumors display an IHC profile that is similar to gastrointestinal tract adenocarcinomas, including expression of CK20, CDX2, and villin and lack thereof for CK7 (Vang et al. 2007). These features would point toward a germ cell origin for the mucinous component rather than metastasis from a gastrointestinal primary. Rarely, the teratoma component is overgrown by the mucinous tumor (Vang et al. 2007).

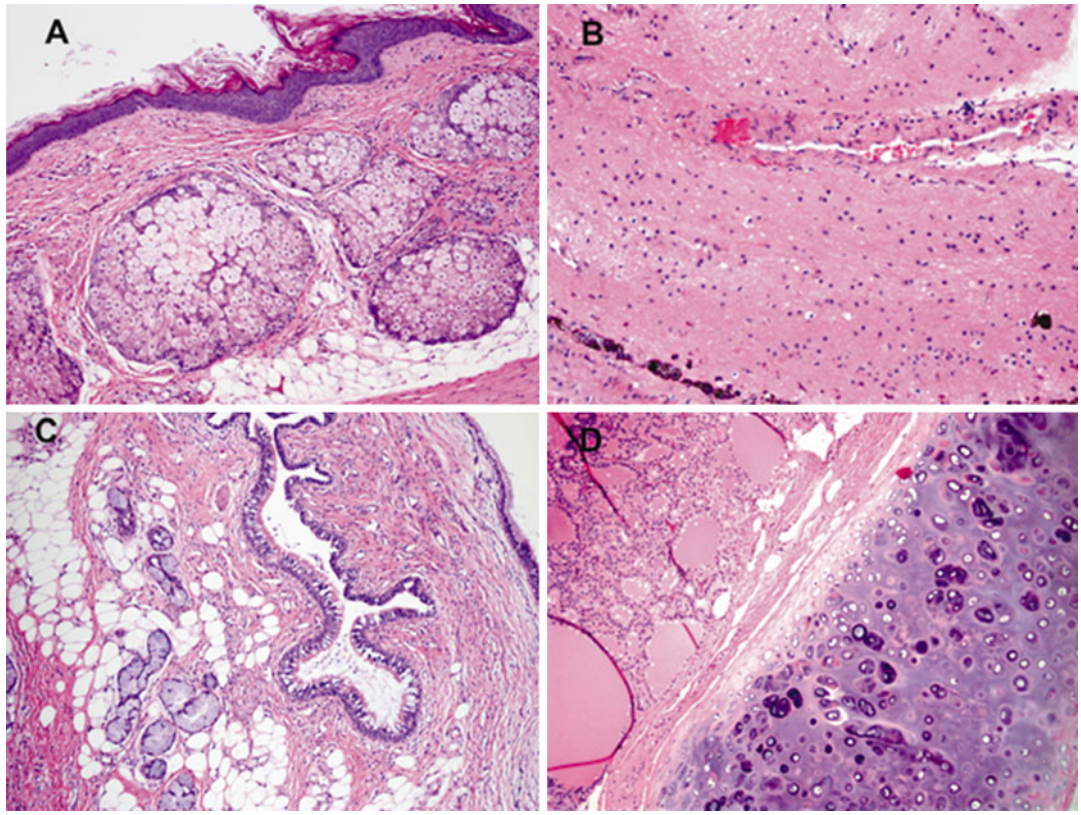

Fig. 2 Mature cystic teratoma containing tissues from all three germ lines. (**a**) Dermoid cyst lined by keratinized squamous epithelium with sebaceous glands in the dermis. (**b**) Mature glial (brain) tissue. (**c**) Glandular type epithelium. (**d**) Cartilage and variable sized colloid filled thyroid follicles (struma ovarii)

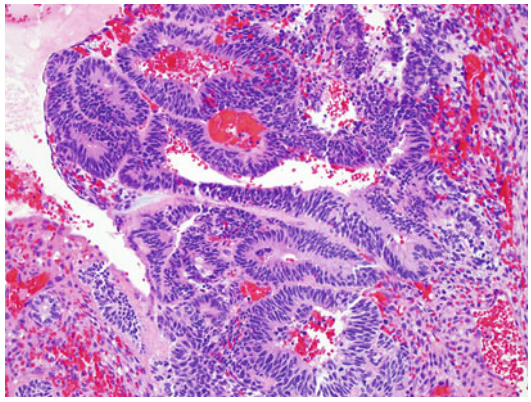

Fig. 3 Immature teratoma containing the diagnostic immature primitive neuroepithelium forming gland-like pseudo-rosettes with palisaded nuclei

4 Immature Teratoma

Immature teratoma is the second (after dysgerminoma) most common MOGCT (Fig. 3). Grossly, the tumors are large, solid, and fleshy with hemorrhage, necrosis, and cyst formation. Immature element (mainly primitive neuroectoderm) is the diagnostic feature of the lesion. Primitive neuroectodermal units are composed of tubules and rosettes. The tubules are lined by atypical, hyperchromatic, stratified cells with frequent mitoses. Immature cartilage, fat, bone, and skeletal muscles are often present but by themselves are not enough to qualify a MCT as immature. Embryoid bodies are the most primitive element in immature teratomas and consist of yolk sac epithelium and germ disk with cells

resembling embryonal carcinoma. In rare instances, the immature element consists of mitotically active cellular glia admixed with ectodermal and endodermal elements (Yanai-Inbar and Scully 1987). Assessment of the degree of immaturity (grading) is a highly reliable prognostic and therapeutic factor (Gershenson 2012). Grading is performed by assessing the relative amount of the immature neuroectodermal component as assessed microscopically. Two-tiered (low and high grade) and three-tiered grading systems are in use (O'Connor and Norris 1994).

The three-tier grading system has been adopted by the most recent World Health Organization (WHO) classification of gynecologic tumors (Prat et al. 2014). Grade 1 tumors contain rare foci of immature elements occupying <1 low power field (x4) in any slide. The immature elements in grade 2 tumors occupy 1–3 low power field in any slide. On the other hand, the primitive neuroectodermal immature elements occupy >3 low power fields in grade 3 tumors (Norris et al. 1976). Any tumor with immature elements occupying more than one low-power field per any slide is a high-grade tumor in the two-tier grading system (i.e., all grade 2 tumors are high grade) (O'Connor and Norris 1994). The two-tier grade system may be more practical since most grade 2 tumors are more comparable in clinical behavior to grade 3 tumors than they are to grade 1 tumors in a three-tiered system. Additionally, unlike grade 1 tumors which are treated conservatively, grade 2 and 3 tumors are treated similarly with recommended chemotherapy (Patterson and Rustin 2006). A point of caution is the occasional presence of normal neuroepithelium in mature teratomas which should not be confused with immature neuroectodermal elements.

4.1 Serum Markers and Immunophenotype

One third of immature teratomas produce AFP. Positive markers include SOX2, SALL4, Glypican-3 (focal), and OCT3/4 (focal) (Liu et al. 2010).

5 Monodermal Teratomas

5.1 Struma Ovarii

Struma ovarii is a monodermal teratoma composed predominantly of thyroid tissue. The tumor occurs most frequently in the fifth decade of life. Clinical hyperthyroidism occurs in <5 % of cases. Grossly, the tumor characteristically appears as greenish brown, firm to slightly gelatinous. Microscopically, struma ovarii varies from a classic macro- and microfollicles with abundant colloid to a cyst with small tubules (Fig. 2d). Solid patterns with hurthle or clear cells may be present and occasionally form trabecular configurations that may mimic carcinoid (Loughrey et al. 2003). The presence of morphologically benign thyroid tissue in the peritoneum (peritoneal strumosis) is now being recognized as a metastatic low-grade follicular neoplasm (Roth and Karseladze 2008).

5.2 Carcinoid Tumor

Carcinoid tumor is a well-differentiated neuroendocrine tumor that arises in MCTs. Grossly, these tumors are brown to tan masses. Microscopically, primary ovarian carcinoids exhibit insular, trabecular, strumal (see below), and goblet cell variants. Insular carcinoids are characterized by tubular glands arranged in garland-like patterns separated by fibrous stroma and sharply defined central lumina with uniform rounded nuclei with fine chromatin stippling (salt and pepper) (Figs. 4 and 5). Trabecular carcinoids display discrete linear cords and trabeculae. The rare goblet cell carcinoids exhibit range of differentiation, including well-differentiated tumors with glands lined by goblet cells in a mucinous background, confluent glands with cribriform or microcystic patterns, and frank carcinomas associated with the carcinoid (Baker et al. 2001).

5.3 Strumal Carcinoid

Strumal carcinoid is a mixed tumor composed of struma ovarii and carcinoid in a background of MCT elements. Grossly, strumal carcinoid

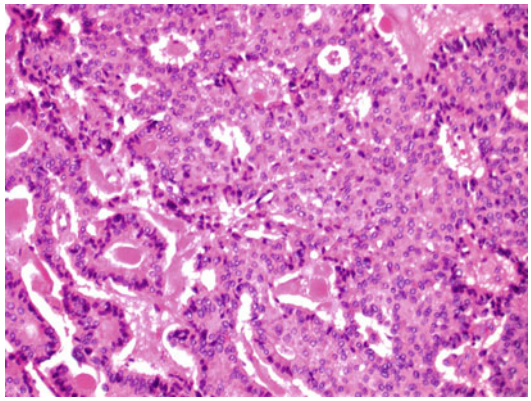

Fig. 4 Insular carcinoid forming broad interconnected sheets of cells

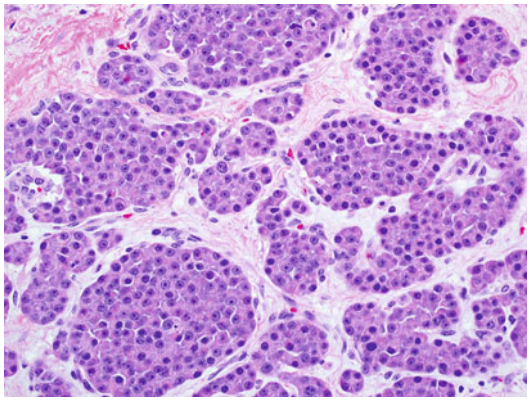

Fig. 5 Insular carcinoid forming sheets of cells with the characteristic granular (salt and pepper) chromatin

exhibits both solid white-to-yellow appearance of carcinoid and fleshy brown areas of thyroid component. Histologically, the carcinoid merges abruptly with the thyroid follicles with variable colloid or both components may be morphologically indistinguishable (Fig. 6). TTF-1, PAX8, and thyroglobulin IHC stains will highlight the thyroid component (Prat et al. 2014).

6 Malignant Transformation in Teratomas

The reported incidence for an associated malignant tumor within an MCT is 1.2–14.2 cases per 100,000 more than 75–90 % of which are squamous cell carcinoma (SCCs) (Fig. 7), especially in

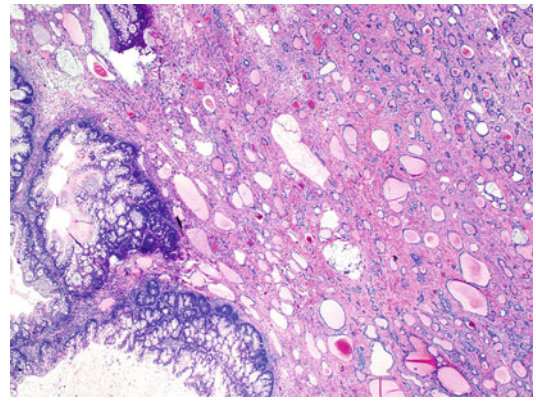

Fig. 6 Mucinous tumor (*left*) and goblet carcinoid (*right*). Notice the admixture of colloid-filled follicles of the thyroid stuma ovarii and the nests and cords of carcinoid component

postmenopausal patients (Hackethal et al. 2008). Wide varieties of other malignancies have been reported including adenocarcinomas (Fig. 8), lymphomas, melanomas, thyroid carcinoma (mainly papillary thyroid carcinoma), and YSTs. Advanced age and larger tumor size are some factors that have been significantly associated with malignant transformation (Desouki et al. 2015).

7 Dysgerminoma

The morphology of dysgerminoma is identical to the testicular counterpart, seminoma and the midline germinoma (Low et al. 2012).

7.1 Epidemiology and Clinical Features

Dysgerminoma comprises 1–2 % of malignant ovarian tumors and is the most common malignant primitive GCT. The tumor occurs almost exclusively in children and young adults, with an average age of 22 years. Patients with gonadal dysgenesis with partial or complete Y chromosome are more commonly susceptible to dysgerminomas arising in a gonadoblastoma (Fig. 9). The overall survival for treated cases is >90 %. Clinical stage and tumor size are the most

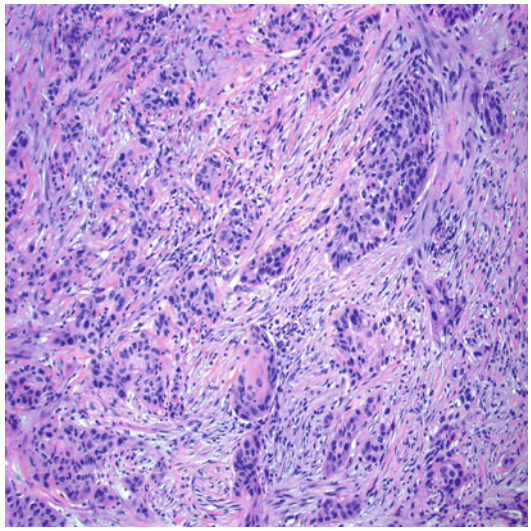

Fig. 7 Invasive squamous cell carcinoma arising in a mature cystic teratoma

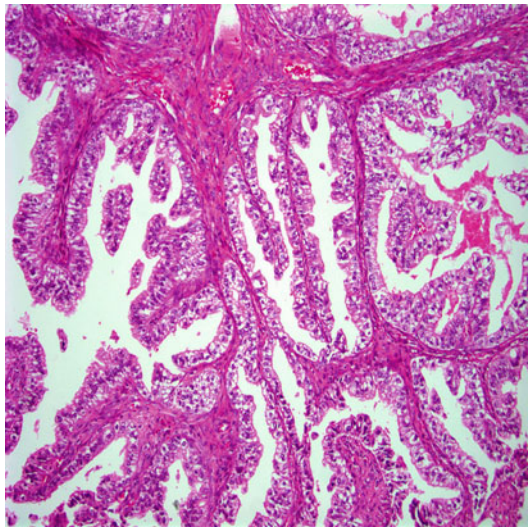

Fig. 8 Invasive adenocarcinoma arising in a mature cystic teratoma

important prognostic factors (de Silva et al. 2004; Prat et al. 2014).

7.2 Gross and Histopathology

The tumors are large with an average diameter of 10 cm. They exhibit solid, tan, or fleshy-white cut surfaces, occasional hemorrhage, necrosis, and cyst formation. Histologically, the neoplastic germ cells are usually arranged in sheets and sometimes grow in individual cords with rare microcysts or pseudoglandular spaces. The tumor is composed of large, clear, primitive germ cells showing no specific pattern of differentiation. The cells are polygonal with abundant eosinophilic cytoplasm and distinct cell borders. The nuclei are uniform with vesicular chromatin, prominent nucleoli, and numerous mitotic figures. The nests of neoplastic cells are surrounded by fibrous stroma with characteristic infiltrating lymphocytes (mostly T cells) (Hadrup et al. 2006; Fig. 9). A minority of cases show a prominent population of syncytiotrophoblasts. Cases with minimal lymphocytic infiltration or an epithelioid eosinophilic cytoplasm should be differentiated from EC and YSTs (Kao et al. 2012). Cases with granulomatous pattern composed of isolated cells embedded in an extensive fibrosis or chronic inflammatory matrix can also represent a diagnostic challenge. Additionally, clear cell carcinomas with solid growth pattern may display morphologic similarity to dysgerminomas (Nogales et al. 2014).

7.3 Serum Markers and Immunophenotype

A small fraction of dysgerminomas (3–5 %) have elevated LDH or low levels of β-hCG. Tumor cells are positive for PLAP, CD117 (c-KIT) (Lau et al. 2007; Fig. 9), D2-40 which is a relatively specific marker (Lau et al. 2007), OCT3/4 (POU5F1), SOX2, and SALL4 by IHC (Liu et al. 2010; Table 2).

7.4 Genetic Abnormalities

Most cases show isochromosome 12p. *C-KIT* mutation has been reported in up to 50 % of cases (Prat et al. 2014).

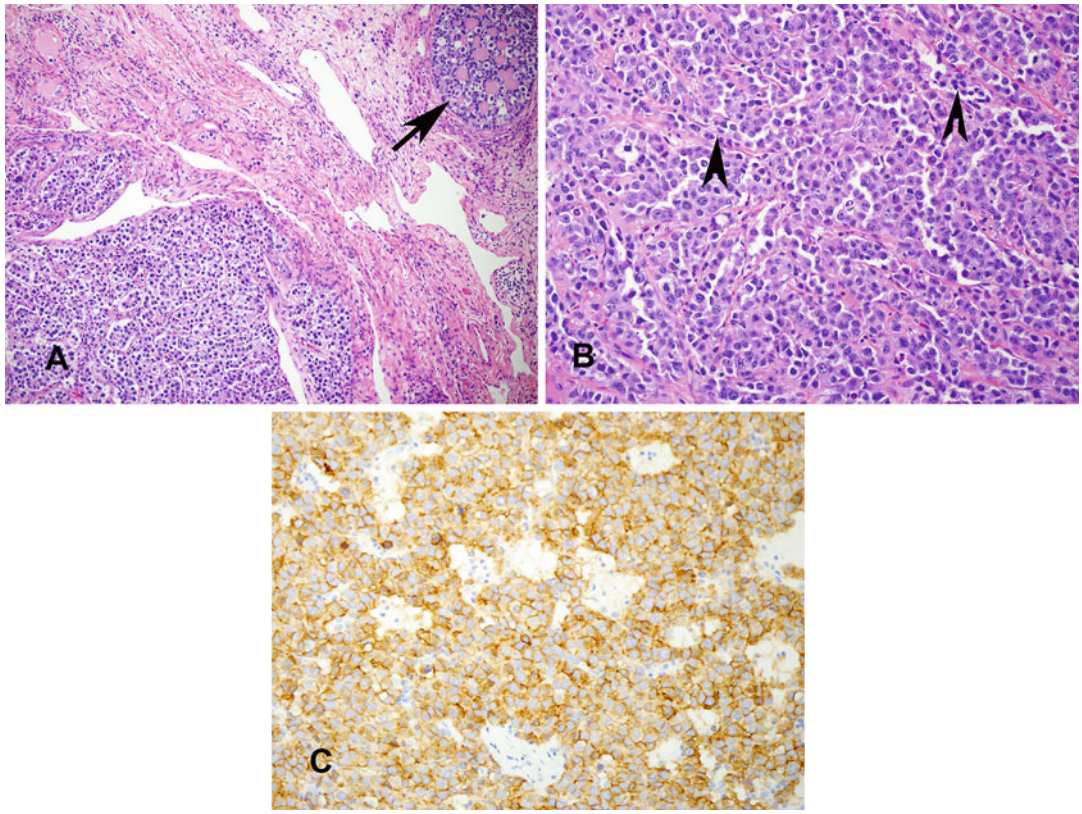

Fig. 9 Dysgerminoma. A germ cell tumor commonly arises in patients with gonadal dysgenesis in a gonadoblastoma (*arrow*) (**a**). The tumor cells grow in sheets of uniform neoplastic cells with centrally placed nuclei and well-defined cell membranes separated by a delicate stroma studied with lymphocytes (*arrow heads*) (**b**). The tumor cells are often positive for CD117 immunohistochemical stain (**c**)

8 Yolk Sac Tumor

YST is a primitive GCT with multiple patterns ranging from primitive gut and mesenchyme to somatic tissue as intestine and liver. These tumors generally have a favorable response to contemporary chemotherapy regimens (de Silva et al. 2004; Nogales-Fernandez et al. 1977).

8.1 Gross and Histopathology

YST is usually a large, soft, encapsulated tumor with gray yellow cut surfaces. Areas of necrosis, hemorrhage, and cyst formation are common. These tumors show complex histologic characteristics comprising early endodermal differentiation into secondary yolk sac elements. Multiple terms have historically been used for these tumors, including endodermal sinus tumors and primitive endodermal tumors. The classic histologic features include reticular microcystic spaces with hyaline globules and amorphous acellular basement membrane like material (Nogales-Fernandez et al. 1977). The cells lining the cystic spaces are clear and flattened that form papillary fibrovascular structures with central blood vessels surrounded by tumor cells and projecting into the space lined by the tumor cells in a characteristic Schiller-Duval bodies (Fig. 10). The stroma is usually myxoid, loose, and hypocellular. Other patterns include polyvesicular type, hepatoid, and intestinal, which are rare and may mimic other neoplasms (Cohen et al. 1987; Kao et al. 2012).

Table 2 Selected immunohistochemistry markers used in the diagnosis and/or differentiation of rare ovarian germ cell tumors

	Dysgerminoma	Yolk sac tumor	Choriocarcinoma	Embryonal carcinoma
HCG-Beta	7 %	0	100 %	23 %
OCT 3/4	70 %	0	0	100 %
Glypican 3	16 %	89 %	78 %	7 %
CD117	92 %	37 %	0	11 %
Alpha- fetoprotein	N/A	69 %	0	31 %
SALL4	53 %	99 %	50 %	99 %
PLAP	96 %	46 %	49 %	100 %
SOX2	67 %	0	0	100 %

The percentage represents the reported positive cases. See text for references
N/A not reported

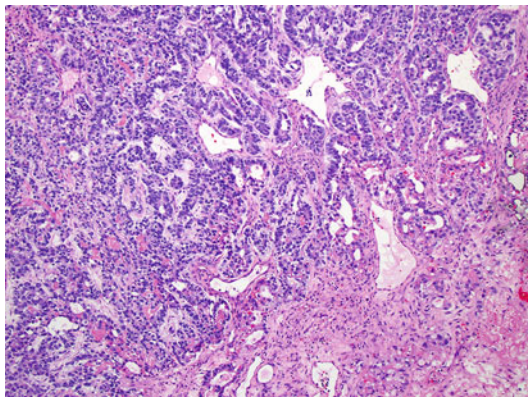

Fig. 10 Yolk sac tumor. The tumor cells grew in microcystic and glandular patterns

8.2 Serum Markers and Immunophenotype

YSTs produce AFP which is considered the gold standard for the diagnosis and follow-up of YSTs. YSTs are positive for AFP, Glypican 3(Kandil and Cooper 2009), SALL4, HepPar-1 in hepatoid areas, CDX2 and villin in intestinal areas, TTF 1, and CD117 by IHC (Liu et al. 2010; Table 2).

9 Embryonal Carcinoma

EC is an extremely rare malignant ovarian germ cell tumor. Due to its rarity, any diagnosis of EC in a female patient should prompt a chromosomal study. Differential diagnosis includes dysgerminoma and YST (Kao et al. 2012; Prat et al. 2014).

9.1 Clinical Features

ECs are aggressive but chemosensitive tumors that occur in children and young adults with an average age of 15 years. Precocious pseudopuberty and isochromosome 12p may be associated with EC (Gershenson 2012).

9.2 Gross and Histopathology

ECs are usually large tumors with an average diameter of 15 cm. The tumors are solid with soft, fleshy cut surfaces with cyst formation, hemorrhage, and necrosis. Histologically, the tumor grows in solid sheets with glandular differentiation. The cells are polygonal with vesicular nuclei, coarse chromatin, and prominent nucleoli. Mitotic figures are numerous. Areas of necrosis and hemorrhage are extensive. Syncytiotrophoblasts are common (Fig. 11; Pallesen and Hamilton-Dutoit 1988).

9.3 Serum Markers and Immunophenotype

EC may produce β-hCG and AFP with the former being more common. ECs are positive for cytokeratin, CD30 (Pallesen and Hamilton-Dutoit

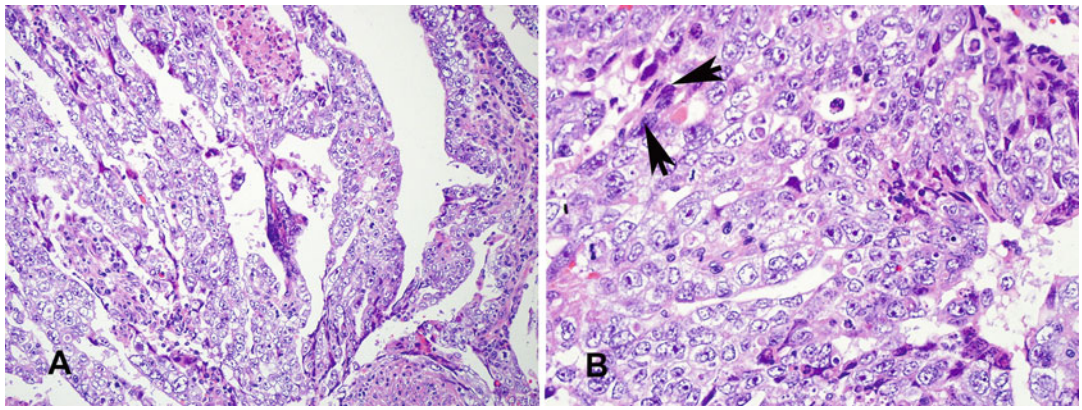

Fig. 11 Embryonal carcinoma. Tumor cells are polygonal and grow in solid sheets (**a**). The cells have vesicular nuclei, coarse chromatin, prominent nucleoli, and frequent mitotic figures (**b**). Notice areas of necrosis and hemorrhage. Syncytiotrophoblasts are common (*arrows*)

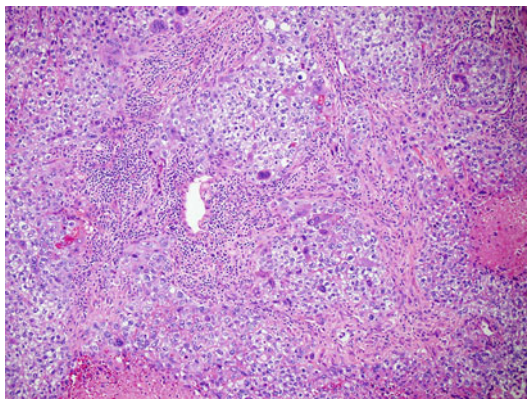

Fig. 12 Choriocarcinoma. The tumor composed of mononuclear trophoblasts and sheets of syncytiotrophoblasts arranged with areas of hemorrhage and necrosis

1988), SOX2, PLAP, OCT3/4, and SALL4 (Liu et al. 2010; Table 2).

10 Choriocarcinoma

Pure nongestational CC is exceptionally rare in the ovaries. These tumors occur mostly in children and young adults (Prat et al. 2014). Grossly, these tumors are large with solid and cystic components, extensive hemorrhage, and necrosis. The tumors show mononuclear trophoblasts and sheets of multinucleated syncytiotrophoblasts arranged in plexiform pattern. Areas of hemorrhage and/or necrosis may be so extensive as to obscure the malignant cells (Fig. 12). β-hCG is a well-known serum marker that is frequently elevated in patients with choriocarcinoma, CC is positive for cytokeratin, β-hCG, α-inhibin (McCluggage 2001), SALL4, CD10, and glypican-3 (Liu et al. 2010; Table 2).

11 Conclusion

Ovarian germ cell tumors develop from primordial totipotential germ and stem cells that can differentiate into extraembryonal and somatic tissues. The most common OGCT is mature cystic teratoma. Dysgerminoma is the most common immature malignant OGCT followed by YST. Clinical information, morphology, and immunohistochemical profile are crucial to assign an ovarian mass to the right category of ovarian tumors.

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Immunohistochemistry of Gynecologic Malignancies

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Abstract

Since its first discovery in 1930, immunohistochemistry (IHC) became a staple in all pathology departments. Its usage gained popularity in early 1970 when "immunoperoxidase" method to formalin paraffin-embedded tissues was developed. In recent days, this ancillary technology becomes a routine and essential tool in diagnostic and research laboratories. Application of IHC in medical practice is commonly used in helping to identify the origin of malignancy, predicting prognosis, and helping select targeted therapy. Gynecologic pathology is not an exception. Example and just to name a few, pair box gene 8 (PAX8) has been used to identify the Müllerian origin of a carcinoma, alpha-inhibin and calretinin for sex cord tumor. In this chapter, we will describe the principle and the interpretation of IHC, and we will discuss various immunomarkers that are commonly used in gynecologic pathology.

Keywords

Immunohistochemistry • Principles • Gynecologic malignancies • Differential diagnosis • Prognostic diagnosis

1 Introduction

Immunohistochemistry (IHC) refers to the process of detecting antigens (e.g., proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in bio logical tissues. These antibodies can be cytoplasmic or nuclear or they can shuttle between the cytoplasm and the nucleus. In recent days IHC has become a routine and essential tool in diagnostic and research laboratories. In this chapter we will discuss the principle, interpretation, pitfalls, and role of the most common immunomarkers in gynecologic pathology.

2 Basic Principle of Immunohistochemistry

Modern immunohistochemistry (IHC) uses an indirect method, so-called "sandwich" method. It consists of three parts, (1) specific antibodies, (2) bridging compound, and (3) detection system that are described below:

1. Specific antibodies, also called primary antibodies, are commonly IgG and less frequently IgM. Specific antibodies react with antigens of interest, and they can be polyclonal or monoclonal antibodies. Polyclonal antibodies are collected from the antisera of immunized animals by antigen(s) of interest. The antisera is then purified and become commercially available for clinical use. They react with multiple epitopes of the same antigen, making them highly sensitive but less specific.

   Monoclonal antibodies are a population of homogeneous immunoglobulin reacting specifically with a single epitope. A monoclonal antibody is manufactured from a so-called hybridoma, a fused and immortalized cell line; a myeloma cell line/fusion partner fused with immunized B-lymphocytes isolated from animal spleen. B-lymphocytes confer the capability to produce specific immunoglobulin, while the fused partner cell line enables immortality and indefinite growth in culture. The advantage of monoclonal antibody comparing to polyclonal antibody is that it is very specific and very consistent.
2. Bridging compound, commonly called "secondary antibody," is a biotinylated nonspecific anti-antibody reacting with primary antibodies. It functions as a link between the primary antibody and detecting systems.
3. The detecting system witnessed significant changes since immunohistochemistry was first introduced. The immunoperoxidase bridging method and the peroxidase anti-peroxidase

(PAP) complex method were used earlier; however, the avidin-biotin is now the dominant method. It consists mainly of the avidin-biotin complex (ABC or BAC). Avidin or streptavidin has strong affinity for biotin with four biotin-binding sites. The biotin molecule is easily conjugated to second antibody and enzyme (peroxidase) then forming the avidin-biotin-peroxidase complex which catalyzes chemical reaction of substrate and chromogens.

2.1 Interpretation of Immunohistochemistry

Immunoreactivity of cells of interest can be nuclear, cytoplasmic, cell membranous, or a mixture of any of these patterns. Positivity of immunostains is defined by specific pattern of immunoreactivity of cells of interest. For example, S100 and TTF1 can be cytoplasmic, but they are considered positive when they exhibit only nuclear immunoreactivity. In general, immunostains can be interpreted for intensity and percentage as well as diffuse, focal, or rare expression. As for intensity, the result of an immunostain is reported as negative or as positive with weak, moderate, or strong intensity. On the other hand, the percentage of positive cells is arbitrary and somewhat subjective.

Immunostains can have false positive and false negative. Causes of false positive can be positive cells that are not the cells of interest, wrong staining pattern (e.g., cytoplasmic instead nuclear), intrinsic peroxidase (commonly seen in inflammatory cells), background staining, and edge effect. Causes of false negative can be loss of cells of interest on deeper cut, bad fixation, loss of antigen during tissue process, and technical problem. To get correct interpretation, it is essential that the pathologist is familiar with tumor morphology and staining interpretation and has good external and internal control. Therefore, experience in surgical pathology and deep knowledge of IHC can avoid these pitfalls.

3 Common IHC Markers Used in Gynecologic Malignancies

3.1 Epithelial Markers

3.1.1 Cytokeratin

Cytokeratin (CK) or simply called keratin is a group of intracytoplasmic proteins of keratin-containing intermediate filaments found in all type of epithelial tissue. It is a common epithelial marker and generally functioning as cytoskeleton. There are 20 common subtypes of keratins. All epithelial cells will express one or more subtypes of keratins. There are two types of keratins: type 1 (acidic) comprising CK 9, 10, 12, and 14–20 and type 2 (basic) comprising CK 1–8. Type 1 and type 2 cytokeratins are in pairs. Cytokeratins can also be divided into low and high molecular weight (LMW and HMW) based solely on their molecular weight. In general, type 1 keratins are low molecular weight keratins, and type 2 keratins are high molecular weight keratins. AE1/AE3 is a cocktail of anti-keratin antibodies. AE1 mainly includes CK10, 11, 13, 14, 15, 16, and 19 and AE3 contains CK1, 2, 3, 4, 5, 6, 7, and 8. It can be slightly variable from manufacture to another. In gynecologic pathology, AE1/AE3 has a cytoplasmic pattern, and it is used to identify cells of epithelial origin, like carcinomas (Fig. 1). However, it also can be positive in some non-epithelial cells like epithelioid leiomyosarcoma and perivascular epithelioid cell neoplasm (PECOMA). The unique CK7 and CK20 expression by carcinomas has been proven to be useful to recognize the origin of these epithelial tumors, and they are regularly used in the IHC workup of malignancies of unknown origin. Tumors of the gynecologic tract are usually CK7+/CK20-, but exception occurs as ovarian mucinous adenocarcinomas can be CK7+/CK20+ (Chu et al. 2000).

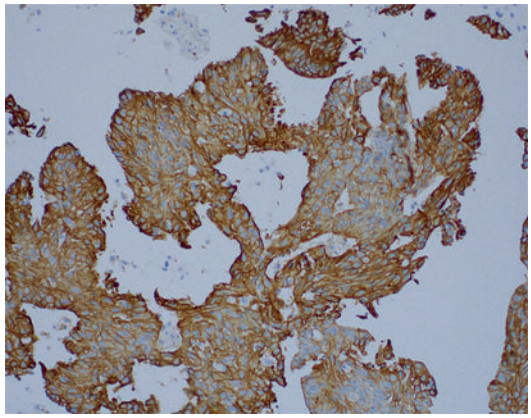

Fig. 1 Total cytokeratin (AE1/3) is positive in a cytoplasmic pattern, indicating that this malignancy is a carcinoma

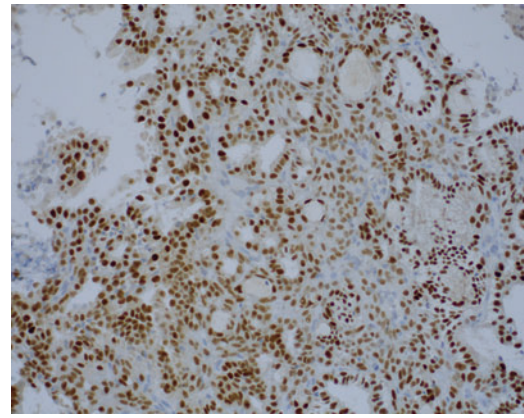

Fig. 2 PAX8 is positive in a nuclear pattern. PAX8 positivity in a tumor of unknown origin indicates that the tumor is of probable gynecologic tract origin

3.1.2 Epithelial Membrane Antigen (EMA)

EMA is another epithelial marker. It is a membrane bound, glycosylated phosphoprotein, the product of the MUC-1 gene (1). It is often expressed in the cytoplasm of nearly all epithelial cells. Therefore it can be used as an alternative or subsidiary to other epithelial marker. However it can also be positive in some non-epithelial tumors, such as sarcoma, namely, synovial sarcoma.

3.1.3 Pair Box Gene 8 (PAX8)

It is a member of paired-box (PAX) family of transcription factors. It is involved in embryogenesis of the thyroid, Müllerian, and renal/upper urinary tracts as a nephric-lineage transcription factor. PAX8 is a nuclear stain that is highly sensitive and site-specific marker for thyroid, Müllerian, renal, and thymic neoplasms (Ozcan et al. 2011). In gynecologic pathology, it has been widely used in identifying tumor of Müllerian origin, including most of ovarian epithelial neoplasms, endometrial carcinomas, and cervical adenocarcinoma (Fig. 2). It is usually negative in cervical squamous cell carcinoma and mesenchymal tumors of the female genital tract.

3.1.4 Wilm's Tumor 1 (WT1)

It is a marker traditionally used to diagnose Wilms' tumor. Wilms tumor protein is a transcription factor encoded by the WT1 gene on human chromosome 11p and serves an essential role in the normal development of the urogenital system. This gene is mutated in a subset of patients with Wilms' tumor. WT1 immunostain gains its popularity in gynecology-pathology due to its nuclear positivity in the vast majority of serous carcinoma of ovary (Fig. 3). Another use of WT1 is to help differentiating endometrial serous carcinoma versus ovarian serous carcinoma, as it is negative in the former and positive in the latter. Because WT1 is frequently positive in mesothelial cells, caution is needed when evaluating malignant cells in peritoneal cytology (Moritani et al. 2008).

3.2 Mesenchymal Markers

3.2.1 Vimentin

It is a type 3 intermediate filament protein that is expressed in mesenchymal cells and the major cytoskeletal component of mesenchymal cells. Therefore, vimentin is often used as a marker of mesenchymally derived cells or cells undergoing an epithelial-to-mesenchymal transition (EMT) during both normal development and metastatic progression. It has a cytoplasmic pattern of expression. In gynecologic pathology it can be positive in endometrial glandular cells and its tumor derivatives. This characteristic feature is very helpful in distinguish adenocarcinoma originating from the endometrium versus the endocervix.

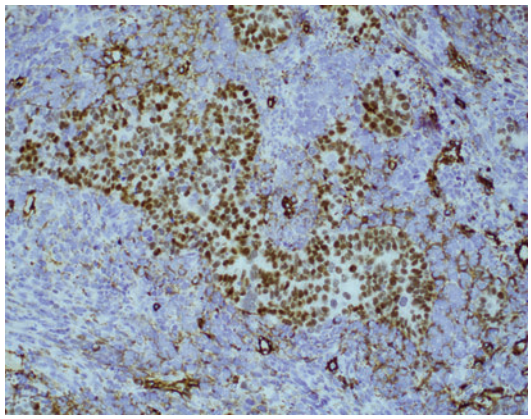

Fig. 3 WT1 is positive in nuclear pattern in a metastatic serous ovarian carcinoma to the vulva

3.2.2 Actin

Actins are microfilaments existing essentially in all eukaryotic cells. They are expressed in many cellular processes, including muscle contraction, cell motility, cell division and cytokinesis, vesicle and organelle movement, cell signaling, and the establishment and maintenance of cell junctions and cell shape. Actins include both alpha-smooth muscle actin (SMA) and muscle-specific actin (MSA) that are equally expressed in skeletal muscle, smooth muscle, myofibroblasts, myoepithelial cells, and pericytes in a cytoplasmic pattern.

3.2.3 Desmin

Desmin is an intermediate filament in skeletal, cardiac, and smooth muscle. Desmin immunostain has a cytoplasmic pattern of expression, and it is useful to identify neoplasms of skeletal, cardiac, and smooth muscle origin, but not for myoepithelial cells, and less than actin for myofibroblasts.

3.2.4 Myoglobulin, MyoD1, and Myogenin

These are skeletal muscle-specific markers often used in identifying rhabdomyosarcoma and rhabdomyosarcomatous component in carcinosarcoma. Myoglobulin is present in well-differentiated skeletal muscle cells.

3.2.5 Transgelin

Transgelin is an actin-binding protein of the calponin family that correlates with smooth muscle differentiation. It is a good marker for smooth muscle differentiation, and recently it proved to be a good marker to differentiate leiomyosarcoma from endometrial stromal sarcoma, where it is positive in the former and negative in the latter.

3.3 Sex Cord Markers

3.3.1 Alpha-Inhibin

Alpha-inhibin is a subunit of an inhibitor of pituitary FSH secretion, encoded by the INHA human gene. Inhibin also participates in the negative regulation of gonadal stromal cell proliferation and has tumor suppressor activity. Alpha-inhibin has a cytoplasmic pattern, and it is widely accepted as a marker for sex cord tumor as it is positive in the vast majority of sex cord stromal tumors such as granulosa cell tumor, Sertoli cell tumor, or a Sertoli cell in Sertoli-Leydig cell tumor. When alpha-inhibin is combined with calretinin (another marker for sex cord stroma tumor), the sensitivity as well as the specificity is highly increased (Deavers et al. 2003; Jones et al. 2010).

3.3.2 CD30

CD30 is also known as ki-1. It is a member of the tumor necrosis family of cell surface receptors and is a lymphocytic activation antigen. It is mostly expressed in classic Hodgkin's lymphoma, large cell anaplastic lymphoma, and embryonal carcinoma of the testis and the ovary.

3.4 Trophoblastic Markers

3.4.1 Human Chorionic Gonadotropin (hCG)

hCG is a polypeptide hormone with two subunits: α- and β-subunits. Naturally, it is produced in the human placenta by the syncytiotrophoblast. β-subunit (β-hCG)-specific immunostain will highlight normal syncytiotrophoblasts, choriocarcinoma, hydatidiform mole, and syncytial trophoblastic cells in tumors containing syncytial trophoblastic cells.

3.4.2 Human Placental Lactogen (hPL)

hPL is another polypeptide hormone produced by syncytial and intermediate trophoblasts. The intensity of immunostain is stronger on intermediate trophoblastic cells than on syncytial trophoblastic cells. Intermediate trophoblastic cells can be positive, but they are most likely negative for hCG. hPL staining is very useful for the diagnosis of placental site trophoblastic tumor due to the predominance of proliferation of intermediate trophoblastic cells in this tumor.

3.5 Other Immunomarkers

3.5.1 Ki67/MIB 1

This marker was originally described in Kiel, Germany, where the name was originated. It is a cellular marker for cell proliferation, and it is encoded by MKI67 gene in human. Ki67 protein is a nuclear protein, and it is present in all cells during the proliferative phases (G1, S, G2, M) and is not present in cells in the resting phase. It has a nuclear staining pattern and provides a proliferation index (Ki67 index). Each given tumor has its own meaningful Ki67 index. In general, the higher Ki67 index associates with more aggressive tumor behavior and worse prognosis. In gynecologic pathology, Ki67 has been commonly used to distinguish between benign and dysplastic lesions of the cervix. It is very useful in differentiating endocervical adenocarcinoma from reactive endocervical glands and in distinguishing squamous cell atrophy from squamous dysplasia of the exocervix.

3.5.2 P53

P53 is an oncoprotein is encoded by TP53 gene that is located on chromosome 17. TP53 is called the "guardian of the genome." It is a tumor suppressor gene and is the most frequently mutated gene in human tumors. In gynecologic pathology, TP53 mutation has been associated with high-grade serous carcinoma. Positive p53 expression in approximately 60 % of tumor cells or greater, or completely negative p53 expression (p53 null) are both indicative for TP53 mutation and, therefore, are considered helpful in confirming high-grade serous carcinoma. P53 immunostain has a nuclear pattern. It can be positive, such as clear cell type and high-grade endometrioid type, and mucinous type.

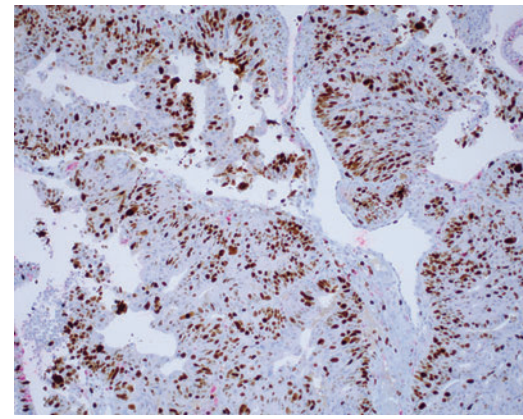

Fig. 4 ER is strongly positive in nuclear pattern in an endometrial adenocarcinoma endometrioid type, FIGO 1

3.5.3 P16

P16 is a tumor suppressor protein and a surrogate marker for high-risk HPV-related neoplasia and carcinoma. A positive result is defined as diffuse, strong nuclear, and cytoplasmic expression by the cells of interest. It is very specific in differentiating squamous intraepithelial neoplasia/carcinoma of cervix from reactive changes. Because of overlapping immunoreactivity with adenocarcinoma of other origin, the use of p16 by itself to identify tumor origin is not of great use.

3.5.4 ER and PR

ER and PR are hormonal receptors seen in the entire female genital tract (Fig. 4). They are used to distinguish endocervical from endometrial cancer where they are negative in the former and positive in the latter. In addition, they are used for therapeutic options in patients with endometrioid adenocarcinoma and endometrial stromal sarcoma.

3.5.5 Insulin-like Growth Factor II mRNA Binding Protein 3 (IMP3)

IMP3 plays an important role in RNA trafficking, stabilization, cell growth, and cell migration during early stages of embryogenesis. IMP3 has a

cytoplasmic and an apical pattern. It is useful to differentiate endometrioid adenocarcinoma from serous carcinoma of the endometrium where it is negative in the former and positive in the latter (Zheng et al. 2008; Mhawech-Fauceglia et al. 2010, 2013).

3.5.6 CD10

CD10 also known as CALLA (common acute lymphocytic leukemia antigen). It is a hematologic marker encoded by the MME gene and is expressed by many hematopoietic malignancies. In the gynecologic tract, it is expressed by the cytoplasm of endometrial stromal cells making it very useful in the diagnosis of endometrial stromal sarcoma (ESS) and for distinguishing ESS from smooth muscle tumor. Other tumors positive for CD10 include many renal cell carcinomas such as clear cell type, solid pseudopapillary type, as well as some urothelial tumors.

4 Application of IHC to Female Genital Tract

4.1 Vulvar Lesions

The most frequent lesion of the vulva is extramammary Paget disease of the vulva and Bowen's disease. Even though melanoma does not commonly occur in the vulva, it is still included in the differential diagnosis (Table 1). It is essential to distinguish among these lesions due to their different treatments and outcomes.

4.2 High-Risk HPV-Related Cervical Neoplasms Versus Benign Reactive Cervical Lesions

High-risk HPV-related cervical neoplasms, squamous and adenocarcinoma, and their precursors are positive for both p16 (strong and diffuse) and Ki67. On the other hand, benign reactive lesions are negative or positive for only one marker but not for both p16 and Ki67.

4.3 Endometrial Endometrioid Adenocarcinoma Versus Endocervical Adenocarcinoma

The panel of immunohistochemistries (IHCs) such as CEA monoclonal, ER/PR, vimentin, and p16 are used to differentiate endometrial adenocarcinoma from endocervical adenocarcinoma. Endometrial adenocarcinomas are positive for vimentin, and ER/PR and endocervical adenocarcinomas are positive for CEAm and Muc1. P16 is unable to differentiate between the two as it is positive in both (Mhawech-Fauceglia et al. 2008; Reid-Nicholson et al. 2006).

4.4 Serous Carcinoma, Endometrial Versus Ovarian Origin

WT1 is very useful to differentiate ovarian serous adenocarcinoma (90 % positive) from endometrial serous carcinoma (90 % negative). WT1 is also useful to distinguish among histologic ovarian subtypes as we will be discussing in the next paragraph (Acs et al. 2004).

Table 1 Immunohistochemistry markers helpful in differentiating among different types of vulvar lesions

		Second Paget disease			
	Primary Paget disease	Anorectal	Urothelial	Bowen	Melanoma
CK7	+ (100 %)	–	+	–	–
CK20	–	+	+ (variable)	–	–
GCDFP-15	+ (88 %)	– (100 %)	– (100 %)	–	–
CEA	+	+	–	–	–
Specific markers	**CAM 5.2**		Thrombomodulin		S100, HMB45 Melanan A
	Androgen		**Uroplakin III**		

Table 2 Immunohistochemistry markers expressions in ovarian surface epithelial malignancies

Carcinomas	WT1 (%)	TP53 (%)	ER (%)
LGSC	100	0	96
HGSC	92	93	80
Mucinous	0	50	6
Endometrioid	4	11	86
Clear cell	0	12	13

4.5 Ovarian Carcinomas Histologic Subtypes

There is no single reliable immunomarker that can distinguish among various ovarian carcinomas histologic subtypes (Baker and Oliva 2004; Kobel et al. 2008). However, a panel of antibodies including p53, WT1, and ER might be helpful (Table 2).

4.6 Clear Cell Carcinoma of Ovary

Clear cell carcinoma (CCC) can be very difficult to diagnose, and other tumors with similar morphology should be excluded:

1. **Metastatic Renal Cell Carcinoma**: ovarian CCC is negative for vimentin and CD10; renal cell carcinoma is positive for vimentin and CD10.
2. **Dysgerminoma:** CCC is positive for AE1/AE3 and EMA; dysgerminoma is negative for AE1/AE3 and EMA.
3. **Yolk Sac Tumor:** AFP and glypican-3 are positive in yolk sac tumor and negative in CCC (McCluggage and Young 2005).

4.7 Mucinous Carcinoma of Ovary Versus Lower Gastrointestinal (GI) Tract

Ovarian mucinous carcinomas are positive for CK7 and either positive or negative for CK20 and CDX2. Mucinous carcinomas of lower GI tract are negative for CK7 and positive for CK20 and CDX2.

4.8 Endometrioid Adenocarcinoma Versus Metastatic Adenocarcinoma from the GI Tract

Endometrioid adenocarcinomas are positive for CK7, ER/PR, and vimentin and negative for CK20 and CDX2. However, metastatic carcinomas from the GI tract are negative for CK7 (except upper GI carcinomas which they are positive for CK7), positive for CK20 and CDX2, and negative for ER/PR and vimentin.

4.9 Endometrial Stromal Sarcoma (ESS) Versus Leiomyosarcoma

ESSs are positive for CD10 and negative or sometime weakly positive for SMA, transgelin, and desmin; leiomyosarcomas are strongly positive for SMA, transgelin, and desmin, and they are negative or occasionally weakly positive for CD10. ER and PR are usually positive in ESS. These immunostains are not usually useful in high-grade ESS and leiomyosarcoma (Hwang et al. 2015).

4.10 Germ Cell Tumors

IHC is very useful and often done to differentiate among germ cell tumors including dysgerminoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma (Table 3). Making the right diagnosis is essential for patient management and outcome.

Table 3 Immunohistochemical markers useful in discriminating among different subtypes of germ cell tumors of the ovary

	Dysgerminoma	Yolk sac tumor	Embryonal carcinoma	Choriocarcinoma
AE1/AE3	− or +weak	+	+	+
EMA	−	+	−	+
CD30	−	−	+	−
CD117	+	+	−	−
OCT-4	+	−	+	−
Glypican-3	−	+	+	+
AFP	−	+	+ in rare cells	
HCG	+ rare cells		+ in rare cells	+

5 Conclusion

IHC is used regularly in medical practices and is commonly used in helping to identify the origin of malignancy, predicting prognosis, and helping select targeted therapy.

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Surface Epithelial Neoplasms of the Ovary

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Contents

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Abstract

Surface epithelial tumors are the most frequent neoplasms of the ovary, occurring in both reproductive and menopausal aged women. They are classified as benign, borderline (low potential malignancy/LMP), and malignant. They are classified in different histologic subtypes, such as serous, endometrioid, mucinous, clear cell, and transitional cell. However, 2014 was a year that brought significant changes to the classification of ovarian tumors. This chapter reviews the latest histologic subtyping of surface epithelial tumors based on the new World Health Organization (WHO) classification and revised grading systems as well as the new International Federation of Gynecology and Obstetrics (FIGO) staging system.

Keywords

Immunohistochemistry • Principles • Gynecologic malignancies • Differential diagnosis • Prognostic diagnosis

1 Introduction

The Surveillance, Epidemiology and End Results (SEER) cancer statistics estimated 21.290 new ovarian cases in 2015 claiming almost 14.180 lives (SEER 2015). Surface epithelial tumors accounts for almost two-third of all ovarian tumors, and they are by far the most frequent ovarian cancer types in the western world. Their

origin is likely the epithelium lining of the ovarian surface, invaginations of this lining into the superficial cortex of the ovary, and/or fallopian tube tissue. Surface epithelial tumor rates are highest in women aged 55–64 years with a median age of 6.3 years. Numerous changes concerning tumor staging and histologic subtypes were introduced in 2014. Based on the new data regarding molecular alterations in ovarian carcinogenesis, the revised WHO classification eliminated transitional cell carcinoma subtype and reclassified them into high-grade serous and high-grade endometrioid carcinoma (Kurman et al. 2014). Second, a seromucinous category was newly introduced. There were also changes made in the 2014 FIGO staging (FIGO Committee on Gynecologic Oncology 2014) that are discussed below.

2 Benign Ovarian Cysts

The most common benign ovarian lesions are the corpus luteal cyst and solitary follicular cyst.

2.1 Corpus Luteal Cyst

Corpus luteal cysts usually occur in women in the reproductive age. They are unilocular cysts. Grossly, the cyst is lined by a convoluted golden brown rim. These cysts can become cystic, and large, filled with chocolate brown fluid (Fig. 1). Histologically, the cysts are lined by large luteinized granulosa cells and an outer layer of smaller luteinized theca interna cells.

2.2 Solitary Follicular Cyst

Solitary follicular cysts occur in women of reproductive age [although they can occur even in postmenopausal women]. They are unilocular cyst with a size ranging from 3 to 8 cm. The cyst lining is composed of an inner layer of granulosa cells and an outer layer of theca interna cells. The evidence of the two layers are seen on reticulin stain where it is negative in former and positive in the later (Fig. 2).

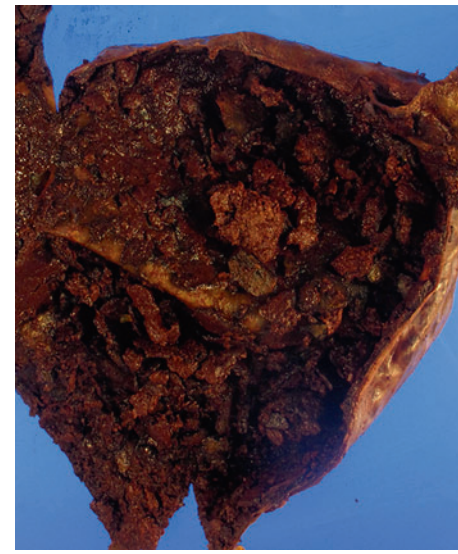

Fig. 1 The ovary is cystically dilated. The cyst is filled with *brown* chocolate fluid with blood clot

3 WHO Classification of Epithelial Tumors

Serous Tumors

Benign

- Serous cystadenoma
- Serous adenofibroma
- Serous surface papilloma

Borderline

- Serous borderline tumor/low malignant potential/atypical proliferative serous tumor
- Serous borderline tumor micropapillary variant/noninvasive low-grade serous carcinoma

Malignant

- Low-grade serous carcinoma
- High-grade serous carcinoma

Mucinous Tumors

Benign

- Mucinous cystadenoma
- Mucinous adenofibroma

Borderline

- Mucinous borderline tumor/low malignant potential/atypical proliferative mucinous tumor

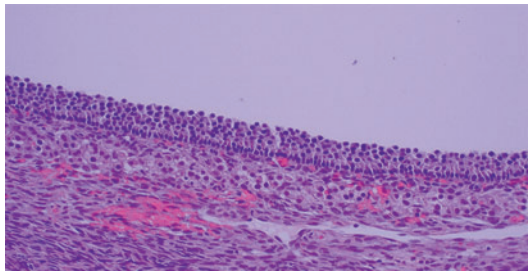

Fig. 2 Solitary follicular cyst where the cyst is lined by inner layer of granulosa cells and an outer layer of theca cells

Malignant
- Mucinous carcinoma

Endometrioid Tumors
Benign
- Endometriotic cyst
- Endometrioid cystadenoma
- Endometrioid adenofibroma

Borderline
- Endometrioid borderline tumor/low malignant potential/atypical proliferative endometrioid tumor

Malignant
- Endometrioid carcinoma

Clear Cell Tumors
Benign
- Clear cell cystadenoma
- Clear cell adenofibroma

Borderline
- Clear cell borderline tumor/low malignant potential/atypical proliferative clear cell tumor

Malignant
- Clear cell carcinoma

Brenner Tumors
Benign
- Brenner tumor

Borderline
- Borderline Brenner tumor/low malignant potential/atypical proliferative Brenner tumor

Malignant
- Malignant Brenner tumor

Seromucinous Tumors
Benign
- Seromucinous cystadenoma
- Seromucinous adenofibroma

Borderline
- Borderline seromucinous tumor/low malignant potential/atypical proliferative seromucinous tumor

Malignant
- Seromucinous carcinoma

Undifferentiated Carcinoma

3.1 Serous Tumors

3.1.1 Serous Cystadenoma and Adenofibroma

Serous cystadenoma and adenofibroma are common tumors accounting for 25% of all benign ovarian neoplasms. It occurs at any age with peak incidence during the fourth and fifth decades [highest at age 40.]. Bilaterality rate is variable and is around 20–30% of cases. Grossly, the cyst is filled with clear serous fluid. The inner layer of the cystadenoma is smooth, while the adenofibroma has focal excrescences. These excrescences are very different than those seen in borderline tumor as they are soft in the later and chalky white and very hard on touch in the former. Microscopically, serous cystadenomas are cysts lined by single cell layer which can be cuboidal or flattened due to the fluid pressure in the cyst content. The stroma may appear as normal ovarian parenchyma or it can be fibrotic. In adenofibroma, the excrescences seen grossly are large broad clefts of fibrous tissue lined by simple single layer of epithelial cells. Some cases have a focal area of pseudostratified epithelium with mild atypia. The tumor is classified as borderline if the pseudostratified epithelium with atypia is present in 10% or more of the tumor. Since this is a very arbitrary cutoff, it has been suggested to classify this finding as a serous cystadenoma with focal epithelial proliferation with a comment explaining the presence of focal areas of borderline tumor

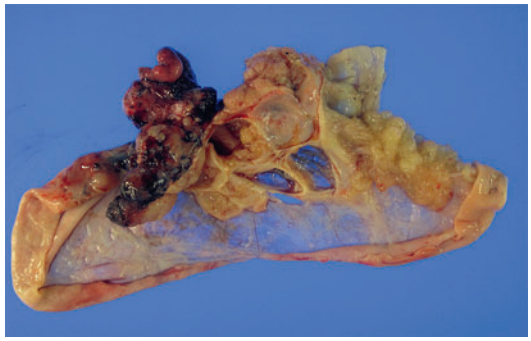

Fig. 3 The ovarian cyst is multilocular. The inner surface is smooth, but some areas of very soft friable vegetations

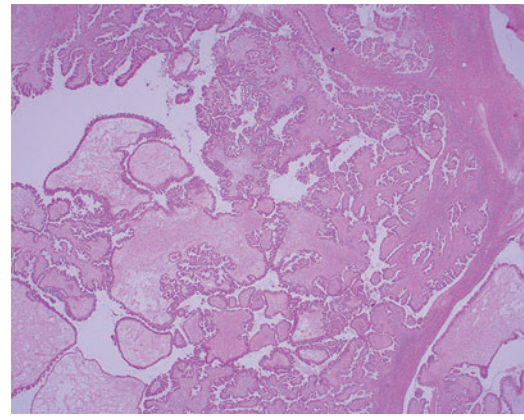

Fig. 4 The cut surface of these projections show papillary structure lined by stratified cuboidal cells. These cells exhibit mild to moderate atypia and few mitotic figures are also present. There is no stromal invasion

which constitute ≥10% of overall histological material" (Longacre et al. 2005).

3.1.2 Serous Borderline Tumor/Low Malignant Potential/Atypical Proliferative Serous Tumor

Serous borderline tumors (SBTs) represent 25–30% of nonbenign serous tumors and occur in women 30–50 years of age. In the majority of cases, they are unilateral and usually present at an early stage (stage I). Grossly, the ovarian mass is typically unilocular although it can present as a multilocular cyst, usually measuring >5 cm. The outer surface of the cyst may appear smooth, but it is important to do a close gross examination to note any surface projections/involvement as it changes the tumor FIGO staging as discussed below. The cyst is usually filled with serous fluid and the cyst lining usually exhibits very soft, friable white projections (Fig. 3). Microscopically, the cyst lining shows papillary projections lined by stratified cuboidal cells. In places, these cells are marked by hobnail features reflected by eosinophilic cytoplasm, mild to moderate atypia, and high nuclear/cytoplasmic ratio. The critical finding of a borderline tumor is the lack of invasion of the ovarian stroma (Fig. 4).

Serous borderline tumor may be associated with omental implants. Peritoneal implants are classified as noninvasive epithelial implants, invasive epithelial implants, or desmoplastic implants. Since implants are a heterogeneous group and various types may coexist, it is important that multiple biopsies of numerous foci of suspicious lesions are done at the time of surgery and that extensive tumor sampling by the pathologist is done to accurately exclude an invasive implant. The diagnosis of peritoneal implants is very challenging and very difficult. It is therefore recommended of the opinion that the final diagnosis is cleared by an expert gynecologic pathologist, especially in cases where the diagnosis may change a patient's treatment options and management.

3.1.3 Serous Borderline Tumor (SBT) Micropapillary Variant (MSBT)

Serous borderline tumors account for 5–10% of all SBTs. Microscopically, MSBT shows highly complex micropapillary growth in a filigree pattern, growing in a nonhierarchical fashion from stalk. It has been described as "Medusa head"--like appearance. Micropapillae are at least five times as long as they are wide (Fig. 5). The significance of this subtype has generated a lot of debate in pathology. Some authors have found a close association between MSBT and invasive implants and have urged that this lesion be labeled as a "micropapillary serous carcinoma." Others prefer the terminology of MSBT, avoiding the use of the term of "carcinoma," to minimize the possibility of overtreating patients (Chang et al. 2008). The general agreement on the significance of micropapillary architecture in

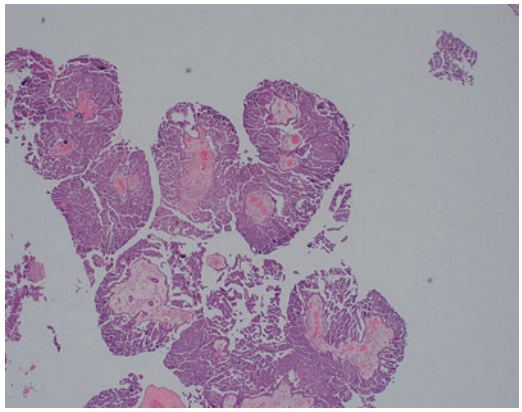

Fig. 5 Serous borderline, micropapillary variant where there is highly complex micropapillary growth in a filigree pattern looking like "medusa head." These micropapillae are long and wide

SBTs is that they are related to significant increases in the incidence of invasive peritoneal implants. Molecular studies show that MSBTs have a similar gene expression profile to low-grade serous carcinomas (LG-serous carcinoma) that are distinct from typical SBT (May et al. 2002). The underlying genes involved in the pathogenesis of LG-serous carcinoma and in MBST include mutations in a number of different genes including *KRAS* and *BRAF*. MSBT is the only surface epithelial-stromal tumor with a well-defined adenoma-carcinoma sequence, whereas LG-serous tumors are thought to arise in a stepwise fashion from a benign cystadenoma (through BST to an invasive LG-serous carcinoma) (Shih and Kurman 2005). Since micropapillary foci of less than 5 mm have no bearing on clinical outcome, these tumors with low levels of micropapillary foci and atypia can be classified as SBT with focal micropapillary features (Slomovitz et al. 2002).

3.1.4 Low-Grade and High-Grade Serous Carcinoma

The majority of epithelial ovarian carcinomas are of serous histology. The new WHO classification of ovarian serous carcinomas places them into two distinct categories: high grade and low grade. The two types are distinct in terms of site of origin, molecular pathways, and treatment response. Low-grade serous carcinomas (LG-SC) are type I tumors that are relatively rare. They are genetically very stable, and they frequently harbor alterations in the mitogen-activated protein kinase (MAPK) signaling pathway. Recent pathologic evidence showed that there are three possible origins for LG-SC: ovarian surface epithelium, fallopian tube origin, and endometrial cells ectopically located in the ovary by retrograde menstruation. They are cytologically very low grade with mild atypia and low mitotic rate. LG-SC are usually cisplatin resistant leading to new clinical trials with tyrosine kinase inhibitors in several cancer centers (Kurman et al. 2014).

High-grade serous carcinomas (HG-SC) are the most common histotype (70%) of the epithelial ovarian cancer. They are considered type II ovarian cancers. They occur in women a bit older than women with SBT, with an average age of 56 years. Patients with serous adenocarcinoma often present with advanced stage disease (stages III and IV) at first presentation. They are characterized by multiple gene abnormalities such as *TP 53* mutation in almost 97%, and BRCA1/BRCA2 loss is frequent (30–45%, including germline and somatic alterations). Many of these tumors are thought to originate from the fallopian tube (serous tubal intraepithelial carcinoma/STIC). Grossly, the tumor varies considerably in size from a few cm to 30 cm (Fig. 6). They can be multicystic or solid. When these tumors are diagnosed at advanced stage frequently, the omentum is replaced by tumor creating what is called "omental caking." Cytologically the tumor exhibits moderate to severe atypia with a high mitotic rate (Mhawech-Fauceglia and Pejovic 2015).

3.2 Mucinous Tumors

3.2.1 Mucinous Cystadenoma

Mucinous cystadenomas are the most common type (75%) of mucinous tumors. They can be very large (up to 20 cm) and can be unilocular or multilocular. They are filled with mucoid fluid and in 95% of cases they are unilateral. The cyst is lined by one layer of cells that have small bland

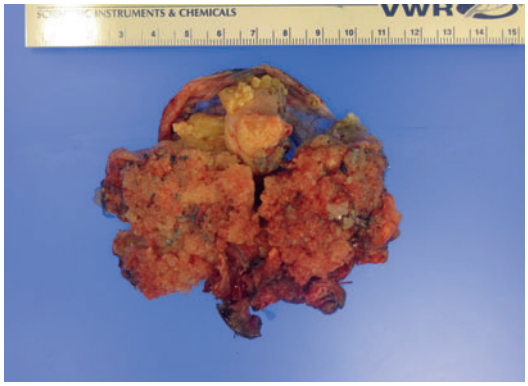

Fig. 6 Ovarian mass with serous carcinoma. The cut surface is partially cystic and partially solid, soft, and friable

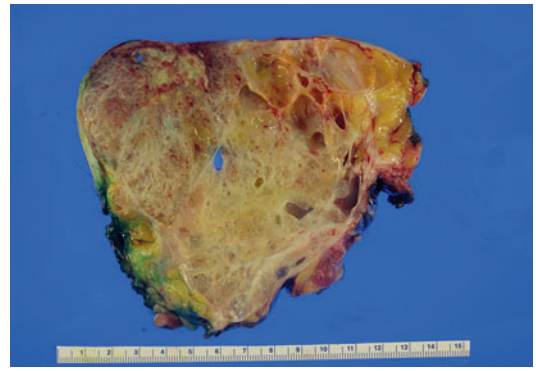

Fig. 7 Cut surface of mucinous adenocarcinoma where it is spongy with numerous tiny cystic spaces. These cysts were filled with mucin

looking nuclei with ample mucin-filled cytoplasm creating what is called "picket fence" appearance.

3.2.2 Mucinous Borderline Tumor/ Mucinous Tumor of Low Malignant Potential

Mucinous borderline tumors (MBT) (mucinous tumors of low malignant potential), as defined by the WHO, are tumors exhibiting an epithelial proliferation of mucinous-type cells greater than those seen in their benign counterparts but without evidence of stromal invasion. MBT can be of intestinal type or endocervical-like type. Mucinous borderline tumors account for 10% of mucinous tumors. They can be multilocular and are bilateral in 40% of the cases. MBT are cystic tumors with a visible solid vegetating mass protruding from the cystic wall. Careful gross examination of the cyst wall to identify these lesions is crucial. Histologically, the lining of the cyst is composed of stratified epithelial cells having high N/C ratio and prominent nucleoli. Goblet cells and Paneth cells are present in the intestinal type. No stromal invasion is seen. Borderline tumors remain a controversial issue concerning their pathogenesis, progression, and treatment (Fischerova et al. 2012).

3.2.3 Mucinous Adenocarcinoma

Mucinous adenocarcinoma (MAC) accounts for 15% of mucinous tumors and 2–4% of all ovarian surface epithelial tumors. They are rare and unilateral in 95% of cases. Therefore, when they are bilateral, metastatic tumors especially from the gastrointestinal tract, namely, the colon, should be in question. They can be very large masses reaching more than 10 cm in the vast majority of the cases. They can be multicyctic/partially cystic and partially solid or solid tumors (Fig. 7). They have two patterns of invasion, the first and most common, pushing or expansile pattern where there are complex glands with back to back architecture and no intervening stroma. The glands are evidently malignant exhibiting mild to moderate cytologic atypia, high nuclear/cytoplasmic ratio, and lack of mucin. The second pattern is infiltrative pattern where single or groups of malignant cells are seen to invade the ovarian stroma with desmoplastic reaction. The origin of MAC is very elusive but some cases have been associated with endometriosis. They harbor Ras pathway alterations, and like LG-SC they may contain a spectrum of mucinous cystadenoma to borderline tumor to MAC in the same tumor (Brown and Frumovitz 2014).

3.2.4 Pseudomyxoma Peritonei

Pseudomyxoma peritonei (PP) is a clinical term used to describe the finding of mucoid, gelatinous material in the abdominal cavity, often

accompanied by an ovarian or gastrointestinal tumor. In 1995, Ronnett et al. classified PP as either a low-grade variety "diffuse peritoneal adenomucinosis" (DPAM) or a high-grade variety "peritoneal mucinous carcinomatosis" (PMCA). The classification of the tumor is prognostically significant with 5-year survival rates of 84% for DPAM and 6.7% for PMCA (Ronnett et al. 2001). PP may originate from an ovarian primary or from an appendiceal primary. Cytoreductive surgery involves removal of the peritoneum and it is common to remove the ovaries, fallopian tubes, uterus, and parts of the large intestine, including the appendix. Whether the primary origin of this tumor is from an ovarian mucinous tumor or from an appendiceal primary or has synchronous origins is still a subject of great debate.

3.2.5 Mucinous Tumors with Mural Nodule

Mucinous tumors of the ovary, whether benign, borderline, or malignant, may contain one or more mural nodules. These nodules are more frequent in borderline and malignant tumors. Grossly, mural nodules are different than the overlying mucinous neoplasm. Grossly, nodules are yellow and pink with areas of hemorrhage and necrosis. Morphologically, they are classified as benign (sarcoma-like) or malignant anaplastic carcinoma and sarcoma. It is important to distinguish between benign and malignant mural nodules, because benign mural nodules are of no prognostic significance (Mhawech-Fauceglia et al. 2015). Whether malignant mural nodules represent a form of dedifferentiation or a collision of two divergent tumor types is still unsolved mystery.

3.3 Clear Cell Tumor

3.3.1 Borderline Clear Cell Tumor

Borderline clear cell tumors are extremely rare. The gross appearance is nonspecific as it can range from solid to spongy. Microscopic findings include a proliferation of small glands with or without cystic dilatation that are lined by flat and hobnail atypical cells. No stromal invasion is present.

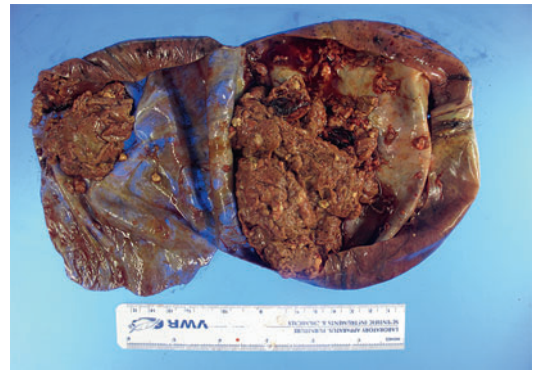

Fig. 8 Cut surface of a clear cell carcinoma. It is unusually cystic. The surface is hemorrhagic and friable

3.3.2 Clear Cell Carcinoma

Clear cell carcinomas (CCC) represent 6–10% of surface epithelial tumors. They occur in postmenopausal women, with a mean age of 57 years. CCC of the ovary have a few notable characteristics. (1) They are almost always unilateral (Fig. 8), and when they are bilateral, a metastatic renal cell carcinoma should be excluded. (2) They are admixed with endometrioid-type adenocarcinoma in 20–25% of cases. (3) They are often accompanied by endometriosis of the same ovary. (4) They may be associated with paraneoplastic hypercalcemia. And (5) they have frequent mutations of ARID1A and PIK3CA genes and express HNF1B. CCC are generally chemoresistant. They have numerous histological patterns including tubulocystic, papillary, solid, or a mixture of any of those patterns. Typically, the cysts are lined by atypical hobnail cells with clear cytoplasm and numerous intracytoplasmic hyaline globules (Fig. 9) (Okamoto et al. 2014).

3.4 Endometrioid Tumors

3.4.1 Endometriotic Cyst

Endometriotic cyst or endometriomas are simply endometriosis cells that have undergone a cystic dilation. They are among the most common

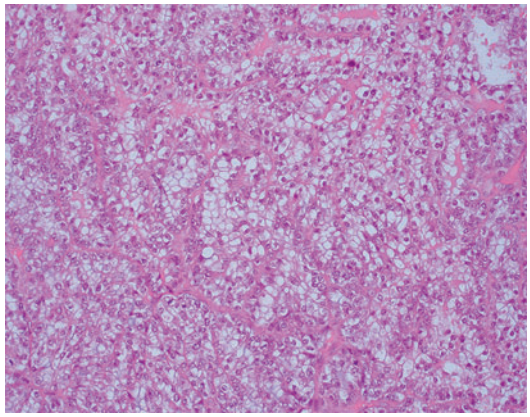

Fig. 9 Microscopic section shows diffuse sheets of tumor cells. These cells have clear cytoplasm. The nuclei are round with prominent nucleoli

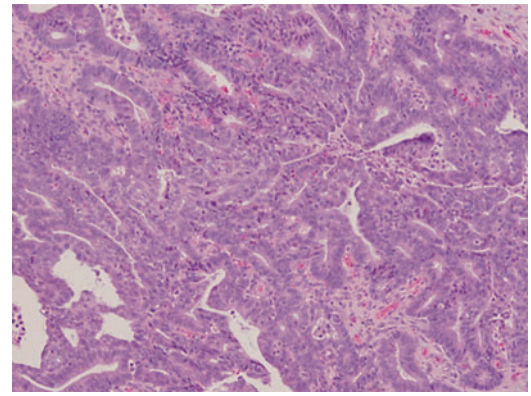

Fig. 10 Endometrioid adenocarcinoma characterized by glands back to back with no intervening stroma

ovarian cystic lesions in the fourth and fifth decade. Grossly, they consist of a large simple cyst. The content is characteristic of chocolate brown fluid. Microscopically, they are a simple cyst lined by cuboidal endometrial cells with hemorrhage, hemosiderin deposits, and macrophages present in the cyst wall.

3.4.2 Borderline Endometriotic Tumor

Borderline endometriotic tumors are such rare tumors that some gynecologic pathologists doubt their existence. Morphologically, they are very similar to endometrial hyperplasia occurring in the endometrium. There are composed of crowded glands that are embedded in very fibrotic stroma. The glands exhibit mild atypia and focal squamous morules.

3.4.3 Endometrioid Adenocarcinoma

Endometrioid adenocarcinoma (EAC) accounts for 10–20% of ovarian carcinomas. They occur in postmenopausal women in the fifth and sixth decade, with an average age of 56 years. They are associated with endometriosis in the same ovary or pelvis, and they can coexist with endometrioid adenocarcinoma of the endometrium in 15–20% of cases. PTEN, CTNNB1, PIK3CA, and ARID1A are commonly mutated in EAC and tumors frequently express estrogen/progesterone receptors and TFF3 by immunohistochemistry (Kobel et al. 2013). They are bilateral in 20% of cases. About half of EAC cases present as low-grade/well-differentiated tumors and with early stage disease (stages I and II). Grossly, the ovary may be cystic or solid with friable cut surface. EAC is microscopically very similar to those occurring in the endometrium, where there is back to back glandular architecture, with no intervening stroma and squamous differentiation in the form of squamous morules and keratin pearls (Fig. 10). However, EAC is the most chameleon ovarian cancer in existence as it can have numerous histologic variants such as tubular/tubulovillous, spindle shape, mucin-rich, eosinophilic, secretory, ciliated, and resembling sex-cord stromal tumors. In these cases, immunohistochemistry is necessary for accurate diagnosis.

3.5 Brenner Tumors

3.5.1 Benign Brenner Tumor

Benign Brenner tumors account for 5% of benign ovarian epithelial tumors. They occur at a wide range group age, between 30- and 60-year-old women. They are usually asymptomatic and can be totally accidental finding. In 20–30% of cases, Brenner tumors develop synchronously with other neoplasms including mucinous neoplasm, dermoid cyst, or mature cystic teratoma. They

are small generally less than 2 cm in size. They are unilateral in 95% of cases. Grossly, they are a sharply delineated mass seen in a normal ovary with a whitish firm cut surface. Microscopically, benign Brenner tumors appear as islands of transitional cells with nuclear grooving embedded in a fibrotic stroma. Sometimes, cystic dilation lined by transitional or mucinous epithelium can be seen. No atypia, mitotic figures, and necrosis are seen.

3.5.2 Malignant Brenner Tumor

Malignant Brenner tumors are the least common of the surface epithelial tumors of the ovary. They occur in women over 50 years of age. They are usually large and they might be cystic or solid. Histologically, they resemble urothelial/transitional carcinoma of the urinary tract. They are composed of sheets of transitional-like epithelium exhibiting moderate atypia and fair numbers of mitotic figures. Cystic areas can be present. With extensive sampling, islands of benign Brenner tumor are seen in the background. However, if no benign Brenner tumor cells are seen after extensive sampling, a high-grade serous or endometrioid adenocarcinoma should be suspected.

3.6 Seromucinous Tumors

Seromucinous tumors is a new entity that was introduced in the 2014 WHO classification. It has three categories: benign, borderline, and malignant (carcinoma). They are rare neoplasms. They are composed of a variable admixture of serous and mucinous (endocervical) epithelial lining. They are likely derived from endometriosis cells but this is still subject to speculation.

3.7 Undifferentiated Carcinoma

By the WHO definition "undifferentiated tumor is a malignant tumor showing no differentiation of any specific Mullerian cell type." Undifferentiated carcinomas usually present at the late stage. They are characterized by proliferation of high-grade tumor cells with high mitotic rate in a diffuse pattern with areas of necrosis.

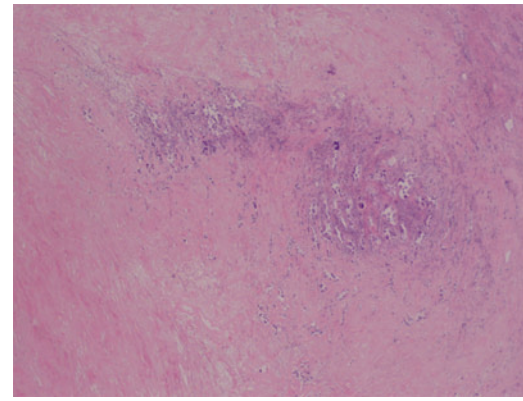

Fig. 11 Residual serous adenocarcinoma post neoadjuvant chemotherapy. Tumor cells are in single files or clusters with abundant fibrous stroma

3.8 Ovarian Carcinoma After Neoadjuvant Therapy

Traditionally, advanced stage ovarian carcinoma is treated by debulking surgery followed by chemotherapy. In some circumstances, neoadjuvant chemotherapy followed by debulking surgery may be done. Neoadjuvant chemotherapy is increasingly being used in the management of patients with advanced ovarian cancer, and pathologists should be aware of the morphologic changes in ovarian cancer after neoadjuvant chemotherapy. Treated tumors may be mistaken for metastatic carcinoma from breast primary or other sites. The morphologic changes seen in response to neoadjuvant chemotherapy include small groups or single tumor cells in a densely fibrotic stroma (Fig. 11). The tumor cells are characterized by nuclear and cytoplasmic alteration making the grading and sometimes the tumor typing impossible and inaccurate. Nuclear changes include nuclear enlargement, hyperchromasia, irregular nuclear outlines, and chromatin smudging. Cytoplasmic alterations include eosinophilic cytoplasm, vacuolation, and foamy cell changes (Fig. 8). The stroma

may have pronounced fibrosis, inflammation, foamy histiocytic infiltrates, hemosiderin deposits, necrosis, calcification, and numerous free psammoma bodies (McCluggage et al. 2002; Miller et al. 2008). Fortunately, tumor cells seem to keep their antigens and therefore express antibodies similar to those seen in pretreatment including CK7+, WT1+, and p53+ (Chew et al. 2009).

3.9 Ovarian Grading Systems

Ovarian cancer is a very challenging task and it is still performed haphazardly with several systems and nonsystems used in different institutes and in different research studies. The lack of uniformity in grading has resulted in little consensus as to whether ovarian tumor grade has any significance in predicting disease outcome. The grading systems used most commonly worldwide are the International Federation of Gynecology and Obstetrics (FIGO) system and the World Health Organization (WHO) system. The FIGO grading system for the ovary is similar to the grading system used in the uterus. It is based on architectural features. The grade depends on the ratio of glandular or papillary structures versus solid tumor growth. Grade 1 is equivalent to <5% solid growth, grade 2 to 5–50% solid growth, and grade 3 to =>50% solid growth. In the **WHO** system, the grade is assessed by both the architectural and cytologic features, without any quantitative evaluation. The Gynecologic Oncology (GOG) system is the most commonly used system in the United States (Bendaj and Zaino 1994). It employs a method based on the histologic type. For example, ovarian carcinoma of endometrioid type is graded similarly to the endometrial adenocarcinoma of endometrioid type. Ovarian carcinoma of transitional type is graded similar to transitional cell carcinoma (TCC) of the bladder. Clear cell carcinomas are not graded at all. Silverberg et al. proposed a new grading system similar to that used in breast carcinoma, and it depends on architectural features (glandular 1, papillary 2, and solid 3), cytologic atypia (mild 1, moderate 2, severe 3), and mitotic rate (1 0–9 mitosis/10HPF, 2 10–24, 3 >25). A score is given by adding the parameters, a score of 3–5 is grade 1, a score of 6–7 is grade 2, and a score of 8–9 is grade 3 (Silverberg 2000). Figure 12 and 13 is an example of grade 1 and grade 3 serous carcinomas. This grading system was confirmed to be reproducible in subsequent studies (Ishioka et al. 2003).

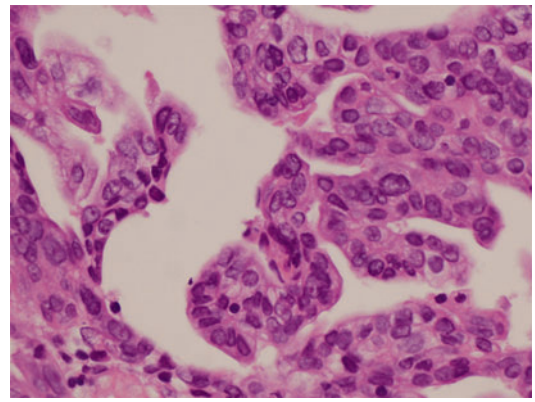

Fig. 12 Low-grade serous carcinoma defined by mild atypia and few mitotic figures

Another study from MD Anderson Cancer Center group suggested adopting a two-tier system that is based primarily on the assessment of nuclear atypia (uniformity vs. pleomorphism) in the worst area of the tumor (Malpica et al. 2004). The tumor is graded into low grade (Fig. 12) and high grade (Fig. 13). A few years after its introduction, the authors confirmed its reproducibility and urged its use to facilitate the clinical trials and protocols (Malpica et al. 2007). This grading system has gained huge popularity and even it was adopted by the 2014 WHO classification. However, this grading could be applied to only serous carcinomas.

3.10 Ovarian Staging FIGO 2014

The International Federation of Gynecology and Obstetrics (FIGO) staging has revised the staging for ovarian cancer, and the approved and new ovarian cancer staging went into effect on 1 January 2014. There were some major differences between the old FIGO and new FIGO staging system.

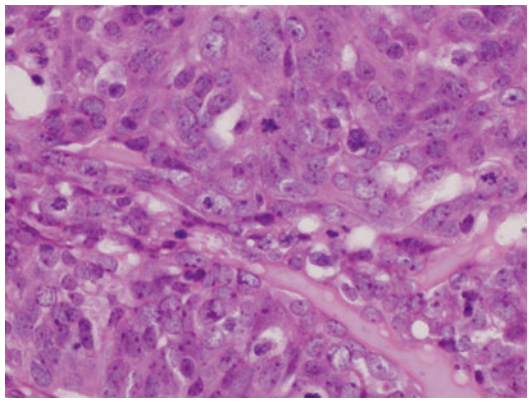

Fig. 13 High-grade serous carcinoma defined by moderate to severe atypia and high mitotic figures

Stage I: IC (ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites) was subdivided in IC1 (surgical spill), IC2 (capsule rupture before surgery or tumor on surface ovarian surface), and IC3 (malignant cells in the ascites or peritoneal washings).

Stage II: IIC in the old system (IIA or IIB with positive washings/ascites) was canceled. So in the new system is only stage IIA and IIB.

Stage III: IIIA was modified and subclassified into IIIA1 (positive retroperitoneal lymph nodes only) and IIIA2 (microscopic, extrapelvic peritoneal involvement ± positive retroperitoneal lymph nodes).

4 Conclusion

Epithelial ovarian tumors are very interesting and fascinating tumors. They still are a subject of debate regarding their pathogenesis, molecular pathways, diagnosis, and treatment. However, the discovery of new genetic mutations and pathways had revolutionized our understanding of ovarian cancer and has provided us with a fresh outlook based on their molecular fingerprints. In the past, histologic classification of surface epithelial tumor had poor interobserver agreement (60%), but because of the advancement of the molecular testing, the immunohistochemistry agreement has risen to 80–90% (Kobel et al. 2010). Due to these advancements in reclassification, it will not be a surprise if 10 years from now, ovarian tumors will be reclassified using not just morphology alone but will heavily incorporate the molecular findings. All the gynecologic oncologic communities are excited about these developments. Targeted therapy and personalized medicine are very promising venues for patients' care.

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Sex Cord–Stromal Tumors of the Ovaries

Mohamed Mokhtar Desouki and Oluwole Fadare

Contents

Abstract

Ovarian sex cord–stromal tumors (SCSTs) are uncommon neoplasms that are known to have a wide morphologic spectrum and which accordingly may be diagnostically challenging. The keys to accurately diagnosing the tumors in this group is to recognize the full pathologic spectrum of every constituent entity and to consider the possibility for each ovarian neoplasm encountered that is plausibly in the differential diagnosis.

Keywords

Ovary • Sex cord–stromal tumors • Fibroma • Fibrothecoma • Fibrosarcoma • Sertoli–Leydig cell tumor • Sertoli cell tumor • Granulosa cell tumor • Leydig cell tumor • Steroid cell tumor

1 Introduction

Patient age, clinical manifestations (e.g., hormone production), morphologic features, and occasionally ancillary diagnostic studies (e.g., immunohistochemistry (IHC)) are important tools in assigning an ovarian neoplasm to one of the tumors among the diverse sex cord–stromal tumors (SCSTs) (Kurman et al. 2014). SCSTs are derived from or display differentiation towards ovarian cortical stroma, hilar, and other steroidal cells and granulosa-theca cells of the ovarian follicles. Apart from fibroma, all other SCSTs are uncommon. The differential diagnosis

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for a given case typically includes many other SCST. Similarly, SCST is frequently in the differential diagnosis for a wide variety of non-SCST. Accordingly, familiarity with the morphologic spectrum of SCST is crucial to their accurate pathologic categorization (Kurman et al. 2014).

2 Epidemiology and Clinical Presentation

SCSTs constitute <10 % of all ovarian tumors. Benign tumors, e.g., fibromas and thecomas account for approximately 85 % of all SCSTs. Adult granulosa cell tumors (AGCTs), Sertoli–Leydig cell tumors (SLCTs), and sclerosing stromal tumors account for approximately 15 % of SCSTs. The remaining tumors collectively are very rare constituting <1 % of the SCSTs (Kurman et al. 2014). Diagnostic issues are mainly due to the rarity of most entities. Clinical information including endocrine manifestations and patient age are important parameters to clinically investigate and communicate to the pathologist. The patient age is especially significant since there are clear age-related differences in the incidence of several tumors in this category: (a) juvenile granulosa cell tumors (JGCTs) occur primarily in the <20 age group (Young et al. 1984a); (b) JGCTs and SLCTs predominate between menarche and 25 years (Young et al. 1982, 1984a); (c) fibrothecomas and AGCTs most commonly occur between 25- and 50-year age group (Burandt and Young 2014; Schumer and Cannistra 2003); and (d) and fibrosarcomas commonly emerge after menopause (Irving et al. 2006; Seidman et al. 1995; Young and Scully 1988). Patients are either asymptomatic with the tumor discovered incidentally on clinical or radiologic examination or present with abdominal pain and/or abdominal mass. Endocrine related symptoms due to hyperestrinism and hyperandrogenism may be the presenting symptoms (Kurman et al. 2014). A small subset of SCSTs have known associations with specific syndromes, including Gorlin's (fibroma), Meigs' (fibroma), Ollier's disease (JGCT), *DICER1* (SLCT, JGCT, gynandroblastoma), Maffucci's (JGCT), and Peutz–Jeghers (sex cord tumor with annular tubules (SCTATs)) (Gorlin 1987; Samanth and Black 1970; Seidman 1996; Young et al. 1982) and may accordingly present with extraovarian manifestations reflecting these syndromes.

Table 1 World Health Organization classification of ovarian sex cordstromal tumors[a]

Pure stromal tumors
Fibroma
Fibrosarcoma
Thecoma
Steroid cell tumor
Pure sex cord tumors
Granulosa cell tumor
Sertoli cell tumor
Mixed sex cord–stromal tumors
Sertoli–Leydig cell tumors
Sex cord–stromal tumors, unclassified

[a]A non-exhaustive listing of commonly encountered tumors in practice (Kurman et al. 2014)

Patient outcomes for SCSTs are largely histotype dependent, although histotypes such as SLCTs and steroid cell tumors may display a wide spectrum of outcomes even within a single diagnostic group. This chapter highlights the most common tumors encountered in clinical practice (Table 1) with an emphasis on the clinicpathologic profile of each entity.

2.1 Fibromas and Cellular Fibromas

2.1.1 Epidemiology and Clinical Features

Fibromas are benign tumors composed of variably cellular neoplasm and collagen deposition. Fibromas with tumors showing thecomatous differentiation (fibrothecomas) constitute the largest group of SCSTs (~85 %). Fibromas commonly affect women in the fifth decade, with a mean age of 48 years. Meigs' syndrome is a constellation of ovarian fibroma, ascites, and pleural effusion (Samanth and Black 1970). Gorlin's (nevoid basal cell) syndrome is another autosomal dominant syndrome described with ovarian fibroma and cutaneous basal cell carcinomas (Gorlin 1987). Cellular fibromas are much less common

than conventional fibromas (10 %) and commonly present with rupture and surface adhesions (Prat and Scully 1981).

2.1.2 Gross Pathology

Fibromas are typically unilateral (9 % bilateral) and range in size from less than 1 to 16 cm (average of 3.8 cm). They typically have a smooth outer surface, solid to rubbery consistency, and white to tan cut surfaces. Edema and calcification are common. Infarction and hemorrhage occasionally present. Fibromas associated with Gorlin syndrome are usually bilateral (~75 %) and more commonly multinodular rather than smooth (Gorlin 1987). Cellular fibromas may have a softer consistency and a tan to yellow color (Young and Scully 1988).

2.1.3 Histopathology

Fibromas are composed of uniformly distributed, bland spindle-shaped cells which usually arrange in a swirling (storiform) pattern. The nuclei are elongated with tapered ends and have inconspicuous nucleoli. No cytological atypia is present, and mitotic figures are usually infrequent (Fig. 1). Calcification, intercellular edema, sex cord–like elements, and hyaline fibrosis may be focally present. The cellularity is typically mild to moderate (Young and Scully 1988).

Cellular fibromas tend to have increased cellularity with haphazard rather than uniform growth pattern with focal areas of conventional fibroma. Usually, no hyaline bands in the hypercellular areas and edema is not as frequent as that of conventional fibromas (Fig. 2). The mitotic index may be >4 per 10 HPF in a subset of cases (Prat and Scully 1981), and these tumors should be categorized as mitotically active fibromas, as long as cytologic atypia is absent.

2.1.4 Differential Diagnosis

Fibromas are easily diagnosed lesions. However, small tumors may be confused with cellular cortex or stromal hyperplasia. These distinctions are based on the presence of a distinct mass lesion separate from the background stroma in fibromas. Pure thecoma is another challenging differential. In contrast to fibromas, thecoma (see below) typically display scattered collagenous plaques and the constituent cells have abundant pale to vacuolated cytoplasm (Young and Scully 1988).

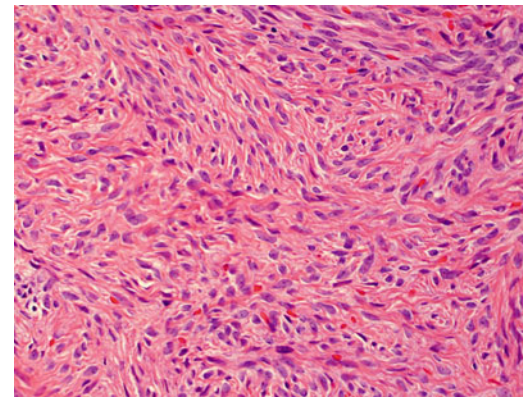

Fig. 1 Ovarian fibroma. The tumor is morphologically characterized by spindled stromal fibroblasts and intervening collagen. No mitotic figures are appreciated

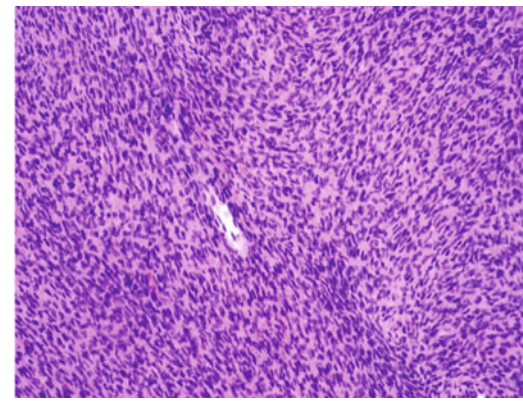

Fig. 2 Ovarian cellular fibroma. Compared to fibroma in Fig. 1, this tumor is hypercellular with vague storiform pattern. No atypia, mitotic figures, or necrosis is seen

2.2 Fibrosarcoma

2.2.1 Epidemiology

Ovarian fibrosarcoma is a rare malignant fibroblastic tumor which occur predominantly in the fifth decade (Prat and Scully 1981).

2.2.2 Gross Pathology

Fibrosarcomas are unilateral tumors which usually reach large size compared to fibromas. Solid

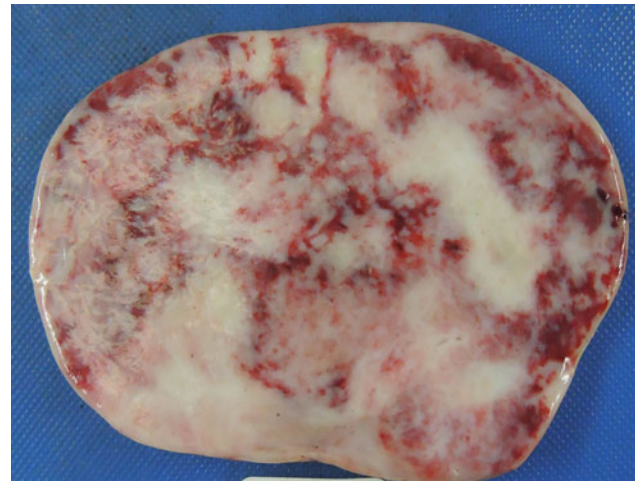

Fig. 3 Ovarian fibrosarcoma. Gross photograph of soft mass with foci of hemorrhage and gross necrosis

to cystic heterogeneous consistency and associated hemorrhage and necrosis are common gross findings (Prat and Scully 1981) (Fig. 3).

2.2.3 Histopathology

Fibrosarcoma, like those of other organs, is composed of spindle cell proliferation with a storiform or herringbone growth pattern with moderate to severe nuclear atypia (Fig. 4). Despite the fact that high mitotic activity is a feature of fibrosarcoma and can be easily found, high mitotic count also encountered in cellular fibromas and by itself is not an indicative of malignancy (Irving et al. 2006; Prat and Scully 1981).

2.2.4 Differential Diagnosis

Fibrosarcomas should be distinguished from other malignant spindle cell neoplasms that may involve the ovary, most notably primary or metastatic leiomyosarcomas or other sarcomas, poorly differentiated SLCTs, or sarcoma-dominant carcinosarcomas.

2.3 Thecoma and Luteinized Thecoma

2.3.1 Epidemiology and Clinical Features

Thecomas are benign tumors that occur typically in postmenopausal women with an average age of 49.6 years. Approximately half of cases will present with manifestations of hyperestrinism. Some cases (~20 %) may be associated with endometrial adenocarcinoma. Another 10 % of thecomas are associated with androgenic symptoms (Burandt and Young 2014). Compared with typical thecomas, luteinized thecomas are more likely to be associated with androgenic manifestations and less likely to be associated with estrogenic manifestations

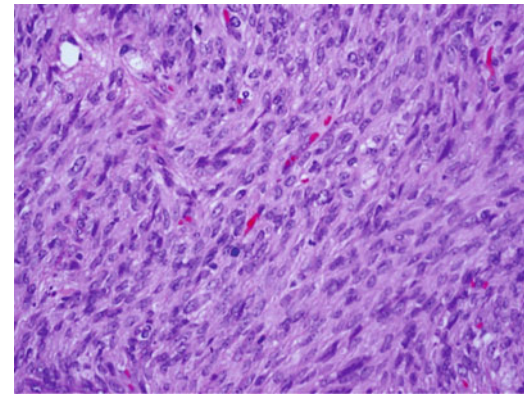

Fig. 4 Ovarian fibrosarcoma. High power (40×) showing increased, cellularity, moderate to severe atypia, and mitotic figures

2.3.2 Gross Pathology

Thecomas are mostly (95 %) unilateral tumors with firm, smooth surfaces and homogeneous yellow and lobulated cut surfaces. The tumor may

reach up to 22.5 cm with an average dimension of 4.9 cm (Burandt and Young 2014).

2.3.3 Histopathology

Thecomas are a group of stromal tumors resembling thecal cells of the ovarian follicles. Pure forms composed of theca cells only with no admixture of fibroblasts (fibrothecomas) or granulosa cells (granulosa-theca cell tumors) are extremely rare. The fusiform tumor cells usually grow in a diffuse pattern with alternating hyaline plaques or rarely in a nodular pattern. The cells have ill-defined membranes and pale gray cytoplasm. Calcifications and keloid-like sclerosis are common in these tumors. Vesicular nuclei with delicate membranes are usually appreciated (Burandt and Young 2014) (Fig. 5).

Luteinized thecomas exhibit single or clusters of lutein cells which are ovoid cells containing abundant cytoplasm interspersed between the neoplastic spindle cells (Fig. 6). Luteinized thecomas in rare occasions are associated with sclerosing peritonitis which typically occurs in women less than 30 years. Patients with this rare association typically present with ascites and bowel symptoms and bilateral ovarian tumors. Morphologically, the peritoneal surface exhibits a fascicular growth pattern with mitotically active but cytologically bland fibroblasts admixed with inflammatory cells (Burandt and Young 2014; Clement et al. 1994). The term "thecomatosis" has been proposed for this phenomenon (Staats et al. 2008).

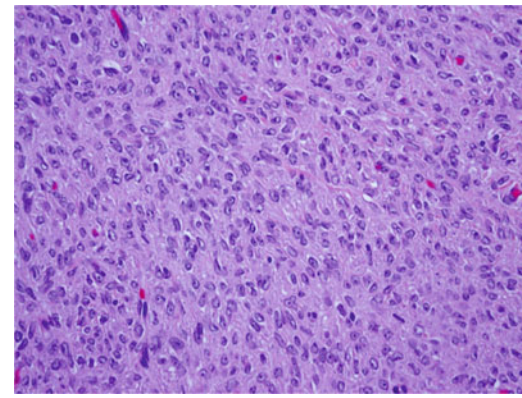

Fig. 5 Ovarian thecoma. The tumor is composed of plump to spindle cells with abundant pale cytoplasm and central nuclei

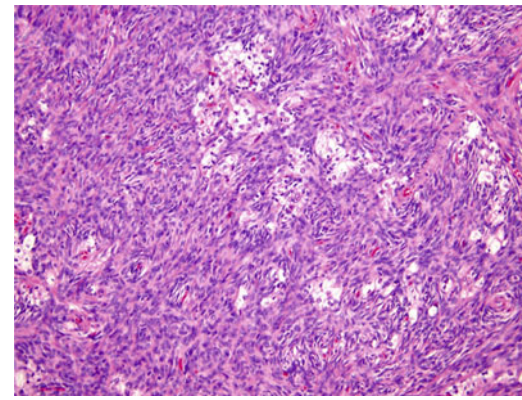

Fig. 6 Ovarian luteinized thecoma. The tumor is composed of fascicles of spindled cells with abundant eosinophilic cytoplasm. Clusters of luteinized cells containing vacuolated cytoplasm are interspersed between the tumor cells

2.3.4 Differential Diagnosis

The differential diagnosis with fibromas has been previously discussed. The cells of GCT, an important differential diagnostic consideration, do not display the pale, eosinophilic cytoplasm of thecomas unless they are luteinized. In comparison to GCTs, reticulin stain will delineate individual cells in thecoma/fibroma (Fig. 7) versus surrounding clusters of cells in GCTs (Burandt and Young 2014) (Fig. 15). Other potential considerations (relative to luteinized thecoma) include stromal hyperthecosis (bilateral, minimal collagen), pregnancy luteoma (commonly multiple, no fibromatous background, minimal lipid), and steroid cell tumor, not otherwise specified (NOS) (a designation that would be used if the spindle cell to steroid cell ratio of the tumor is less than 1:10)

2.4 Steroid Cell Tumors

This group of tumors are very rare constituting less than 1.0 % of all SCSTs. The group includes hilus cell tumor, stromal luteoma, Leydig cell tumor, pregnancy luteoma, and lipid cell tumor. The term "lipid cell tumor" is not recommended

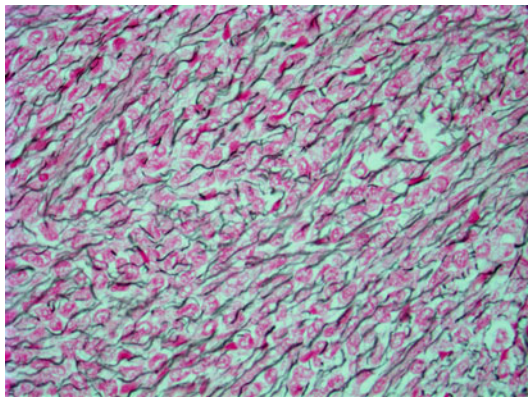

Fig. 7 Reticulin special stain. A reticulin stain surround individual cells in fibrothecoma

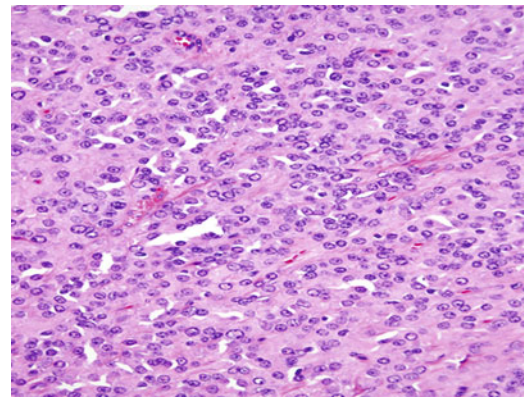

Fig. 8 Ovarian Leydig cell tumor. Aggregates of eosinophilic cells with centrally located nuclei and abundant cytoplasm

because it is nonspecific since most of these tumors contain lipid in the cytoplasm (Seidman et al. 1995). The pregnancy luteoma is considered by some as an exaggerated hyperplasia of thecalutein during pregnancy rather than a neoplasm (Norris and Taylor 1967). The most recent World Health Organization (WHO) classification of tumors of the female reproductive organs included Leydig cell tumors and steroid cell tumors under this category (McCluggage et al. 2014).

2.4.1 Clinical Manifestations

Leydig cell tumors occur in the sixth and seventh decades with symptoms related to hormone production mainly testosterone in most cases in the form of hirsutism (Zhang et al. 1982). The tumors are typically unilateral and relatively small in size. The biology of most of these tumors is favorable with benign behavior (Zhang et al. 1982). On the other hand, the age range of patients with steroid cell tumors, NOS is very wide with a mean age of 43 years. Steroid cell tumors, NOS are typically unilateral with a mean diameter of 8 cm. The behavior of steroid cell tumors NOS have a guarded prognosis with a reported rate of 34 % with malignant behavior (Hayes and Scully 1987).

2.4.2 Steroid Cell Tumor Types

Leydig Cell Tumor

Leydig cell tumor occurs mostly in the hilus of the ovary or rarely in the ovarian parenchyma. Crystalloids of Reinke should be present to qualify for this classification otherwise the tumor will be classified as steroid cell tumor. The crystalloids of Reinke are rod or spherical eosinophilic structures in the cytoplasm. Histologically, Leydig cell tumors exhibit lobular aggregates of eosinophilic to vacuolated cells with centrally located nuclei and abundant cytoplasm (Fig. 8). Additionally, anuclear eosinophilic material intervening the cells is a clue to the diagnosis. Nuclear atypia in the form of enlarged, bizarre nuclei is not uncommon and does not imply malignant behavior (Zhang et al. 1982).

Steroid Cell Tumors, Not Otherwise Specified

Absence of crystalloid of Reinke is the main morphologic feature which qualifies for this nomenclature (Hayes and Scully 1987). Worrisome (malignant) features include large size (>7 cm), high mitotic index (> two per 10 HPFs), necrosis, and severe nuclear atypia (Hayes and Scully 1987). The gross morphology is yellow to dark brown (Fig. 9). The cells form diffuse aggregates in linear or circular pattern separated by thin fibrous septae. The nuclei are centrally placed with prominent nucleoli and minimal atypia. The cytoplasm is frequently vacuolated and lipid rich (Hayes and Scully 1987) (Fig. 10).

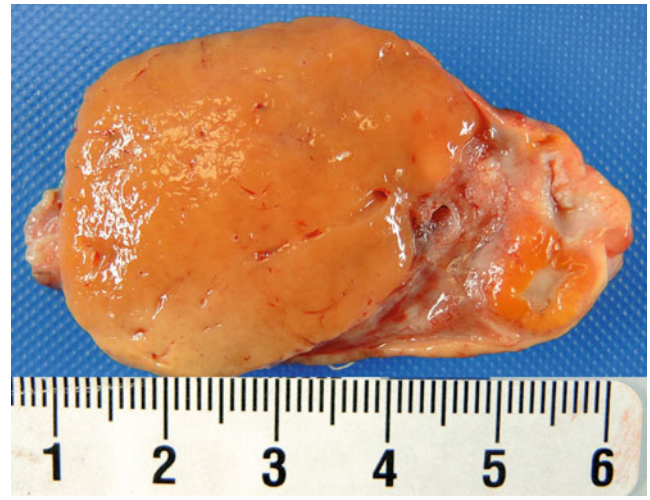

Fig. 9 Ovarian steroid cell tumor. Gross photograph showing well circumscribed yellow mass

Stromal Luteoma

This tumor presents with estrogenic symptoms mainly vaginal bleeding and a few cases present with androgenic symptoms. The lesion is characterized by centrally located neoplasm within the ovarian parenchyma. A uniform cell population with centrally placed nuclei and prominent nucleoli are evident. The cytoplasm is pale, finely granular, pink to vacuolated with demarcated cellular outlines (Fig. 11). Hyperthecosis with vacuolated cells in the surrounding ovarian stroma is common (Vilain et al. 1992).

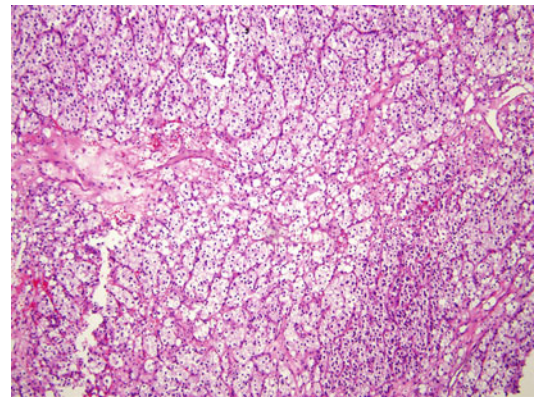

Fig. 10 Ovarian steroid cell tumor, not otherwise specified. The cells form diffuse aggregates separated by thin fibrous stroma. The cytoplasm is vacuolated and lipid rich. The nuclei are centrally placed with prominent nucleoli

2.5 Granulosa Cell Tumors

Granulosa cell tumors (GCTs) are rare tumors constituting 1–2 % of all ovarian tumors. The tumors contain at least 10 % of follicular granulosa cells. Despite the fact that GCTs are rare, they are the second most common SCSTs after fibromas (Schumer and Cannistra 2003).

2.5.1 Clinical Features

Traditionally GCTs are classified into adult and juvenile types. As the name implies with exceptions both ways, adult type predominates in postmenopausal women and juvenile type in younger age (average age of 13 years) (Schumer and Cannistra 2003; Young et al. 1984a). The tumor may produce estrogenic or androgenic effects, including abnormal uterine bleeding with cystic hyperplasia due to anovulation. Associated endometrial carcinoma have been reported in ~5 % of cases with GCTs. Juvenile GCTs are rarer (less than 5 % of GCTs) and commonly associated with hyperestrinism resulting in isosexual pseudoprecocity in prepubertal girls (Young et al. 1984a).

2.5.2 Gross Pathology

GCTs are unilateral in ~91 % of cases, and stage I is the most common stage at diagnosis. Grossly, GCTs are typically solid with variable cystic spaces and hemorrhagic. Tumors with prominent

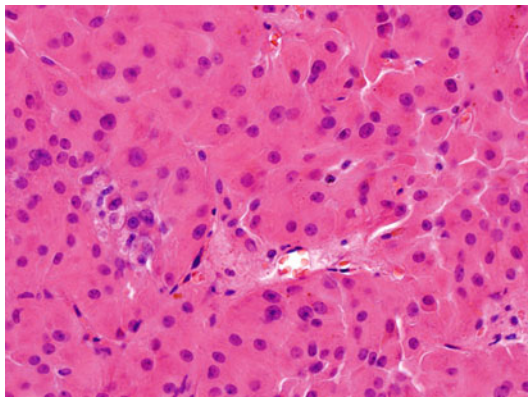

Fig. 11 Ovarian stromal luteoma. The tumor composed of a uniform cell population with centrally placed nuclei and prominent nucleoli. The cytoplasm is finely granular with demarcated cellular outlines

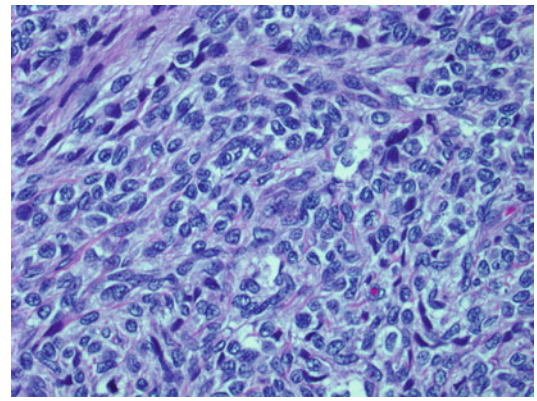

Fig. 12 Adult granulosa cell tumor of the ovary. The tumor composed of monotonous cells with scant cytoplasm, uniform nuclei with evenly dispersed chromatin and nuclear grooves

theca component are often yellow and firm. Rupture at the time of surgery is not uncommon and do occur in up to 15 % of cases (Schumer and Cannistra 2003; Young et al. 1984a).

2.5.3 Histopathology

Adult GCTs exhibit a range of epithelioid to spindle cell pattern with organoid or diffuse architecture. Combination of patterns is usually seen in a single tumor. Morphologic patterns include trabecular, insular, gland-like, microfollicular and macrofollicular, diffuse, "watered silk," pseudopapillary, and cystic. The nuclei are uniform, with evenly dispersed chromatin and nuclear grooves (Figs. 12 and 13). Call–Exner bodies are characteristic of GCTs and defined as granulosa cells which arrange haphazardly around a space filled with eosinophilic material. Focal marked atypia is more common in juvenile GCT and is not independently correlated with malignant behavior. Luteinization of cells with plump pale cytoplasm is a common finding (Schumer and Cannistra 2003).

The morphology of juvenile GCT is characterized by a nodular or diffuse proliferation of neoplastic cells in a myxoid and edematous background. Follicle-like spaces of different sizes and shapes containing proteinaceous material are characteristic with rare Call–Exner bodies (Fig. 14). In contrast to adult GCTs, the nuclei are

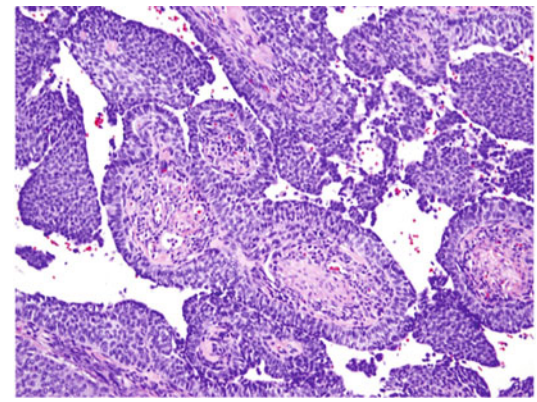

Fig. 13 Adult granulosa cell tumor of the ovary. The characteristic tumor cells grow in a pseudopapillary pattern

larger and hyperchromatic with no to scarce grooves (Young et al. 1984a). JGCTs are known to display a notably higher mitotic index than AGCTs, whose mitotic index is generally <5 MF/10 HPF. GCTs stain positive for inhibin, and FOXL2 by IHC. Reticulin stain usually surrounds nests and groups of cells (Fig. 15).

2.5.4 Differential Diagnosis of GCTs

- High grade endometrioid adenocarcinoma. Carcinomas usually exhibit a higher nuclear grade, are more mitotically active than the typical AGCT, and by IHC are negative for sex cord–stromal markers and are positive for epithelial membrane antigen (EMA).

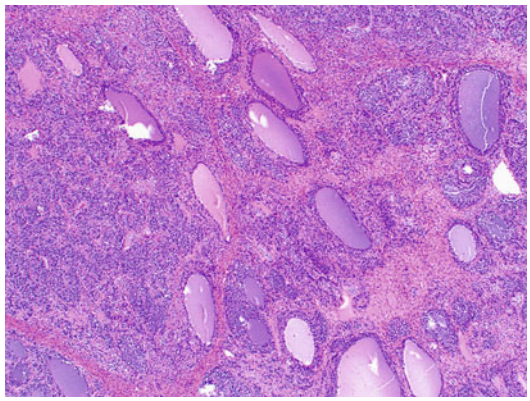

Fig. 14 Juvenile granulosa cell tumor of the ovary. Diffuse proliferation of tumor cells among follicle-like spaces of different sizes and shapes

- Metastatic lobular carcinoma of the breast. Lobular carcinoma grows in cord-like and single file patterns, typically involves both ovaries and is EMA and GATA3-positive and is negative for inhibin and FOXL2.
- Carcinoid tumor. Insular pattern carcinoid is usually associated with teratoma, the nuclear chromatin is granular "salt and pepper," and the cells are positive for neuroendocrine markers, e.g., synaptophysin and chromogranin.
- Luteinized thecoma/fibrothecoma. A reticulin stain will surround individual cells in fibrothecoma and nests of cells in GCT (Figs. 7 and 15).
- Small cell carcinoma, hypercalcemic type (SCCH). Hypercalcemia and lack of estrogenic manifestations may help in differentiating this tumor from the juvenile GCT. Morphologically, SCCH lacks the nodular growth pattern of JGCTs, shows a lesser tendency for follicle-like spaces, mucinous cells in a subset, lacks inhibin and FOXL2 positivity, and shows loss of SMARCA4 (BRG1) expression.
- Undifferentiated carcinoma. More mitotically active than most AGCTs and are negative for inhibin and calretinin.
- Other entities. Endometrioid carcinoma with sex cord elements, endometrioid stromal sarcoma, SCTATs, gonadoblastoma, melanoma, steroid cell tumor, and yolk sac tumor.

2.6 Sertoli–Leydig Cell Tumor

SLCTs differentiate towards testicular counterparts. These tumors are rare, usually unilateral and classified according to the tumor grade and associated morphologic changes (Young and Scully 1985).

2.6.1 Epidemiology and Clinical Features

SLCTs predominate in the third decade with an average age of 25 years (Young and Scully 1984). Androgenic symptoms, e.g., virilism, amenorrhea, deepening of voice, and clitoromegaly are the main symptoms in approximately half of patients (Young and Scully 1985).

2.6.2 Gross Pathology

SLCTs tend to be partially cystic mass and some may be either completely cystic or completely solid. Solid tumors are yellow with lobulated outer surfaces. Higher grade lesions show gross hemorrhage and necrosis. As the case with GCTs, SLCTs present at an early stage at initial diagnosis (Young and Scully 1985).

2.6.3 Histopathology

SLCTs are classified according to tumor differentiation and clinical behavior into well-differentiated (11% of cases, clinically benign), intermediately differentiated (54 % of cases, 11 % malignancy rate), and poorly differentiated (11 % of cases, 59 % malignancy rare) (Young and Scully 1985).

Well-Differentiated

The neoplastic cells form tubules forming either compact lobules of round tubules, or tubules which are infiltrative between the intervening collagen bundles. The tubules usually have open lumina and rarely are compact with inconspicuous lumens. The Leydig cells are present throughout the tumor with variable density in a single or cluster pattern (Young and Scully 1984). The tubules are lined by cells with elongated nuclei arranged perpendicular to the surrounding basement membranes. The cytoplasm is uniform and

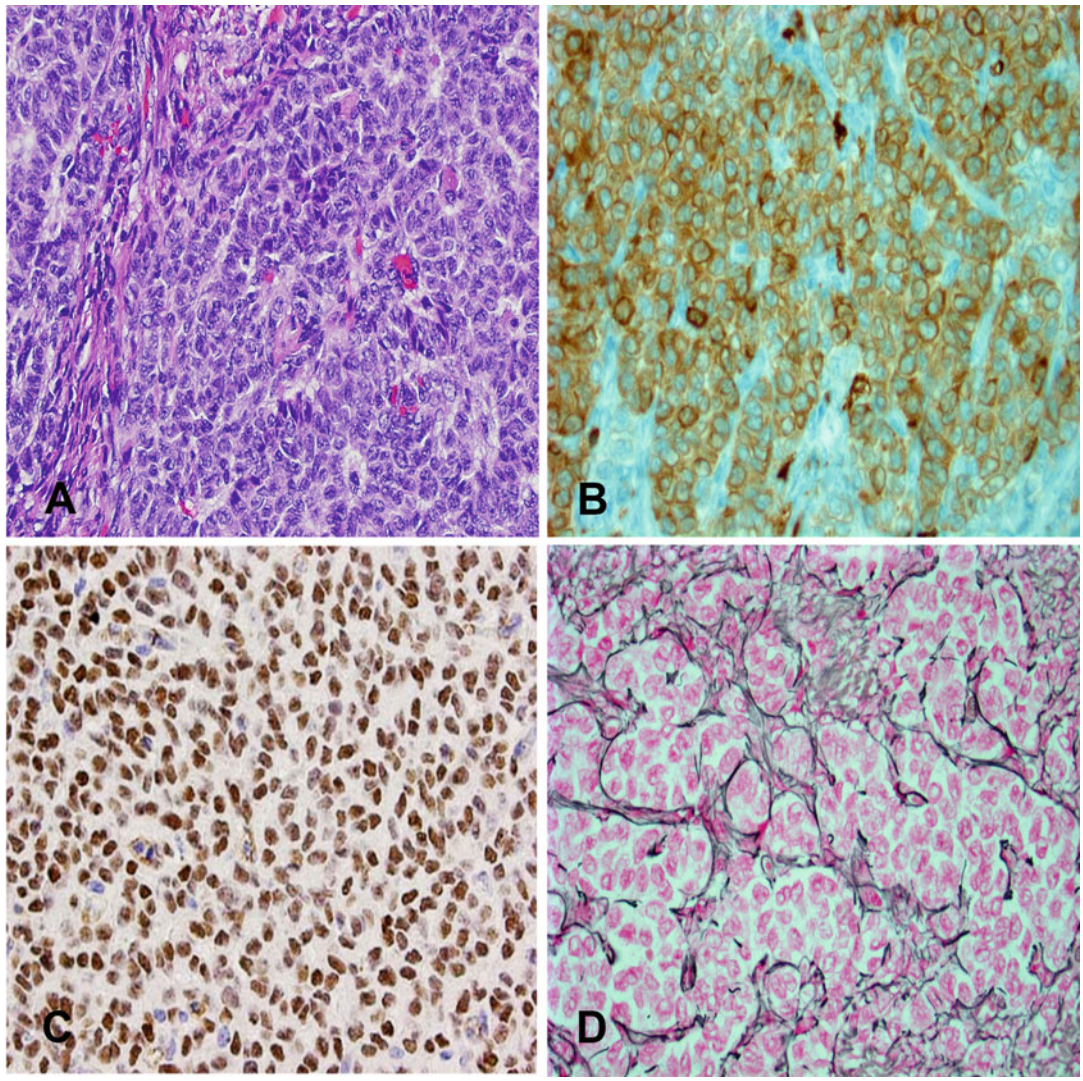

Fig. 15 Adult granulosa cell tumor of the ovary. (**a**) The tumor composed of monotonous cells with uniform nuclei which stain positive for inhibin (**b**) and FOXL2 (**c**) by immunohistochemistry. (**d**) Reticulin stain surrounds nests of cells

may be lipid rich or oxyphilic (Ferry et al. 1994) (Fig. 16).

Intermediately Differentiated

The characteristic morphology is the presence of alternating cellular areas separated by hypocellular edematous stroma in lobulated pattern. The neoplastic cells grow as sheets, tubules, nests, cords, or microcysts. The cells have small, round nuclei and scant cytoplasm. Leydig cells are usually rimming the nodules at the periphery and populating the hypocellular stroma (Young and Scully 1985) (Fig. 17).

Poorly Differentiated

These tumors are characterized by sarcomatoid growth pattern. They are formed of spindle cells mimicking sarcoma with high nuclear grade and absent tubule formation. Leydig cells are rare. Inhibin stain by IHC (see below) is positive (Young and Scully 1985) (Fig. 18).

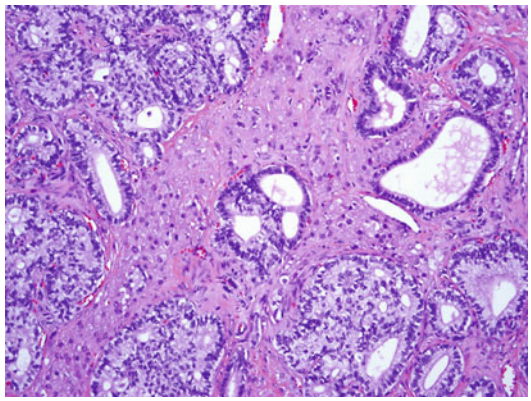

Fig. 16 Well-differentiated Sertoli–Leydig cell tumor. The neoplastic cells form tubules with elongated nuclei which arrange perpendicular to the basement membranes. The cytoplasm is uniform and contains lipid. The Leydig cells are present throughout the tumor

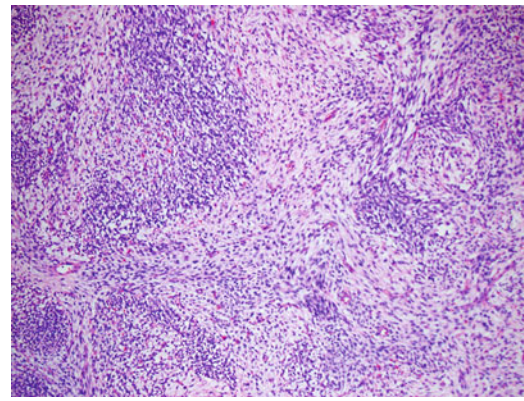

Fig. 17 Intermediately differentiated Sertoli–Leydig cell tumor. The characteristic morphology is shown in this photomicrograph with alternating cellular areas separated by hypocellular edematous stroma in lobulated pattern. The cells have small, round nuclei and scant cytoplasm. Leydig cells are scattered in the hypocellular areas

SLCT with Retiform Pattern

These tumors as the name implies are characterized by growth pattern simulating the rete testis. Morphologically they include poorly formed tubules, gland-like structures, and intraglandular micropapillary pattern. The papillae are short and blunt with hyalinized cores.

SLCT with Heterologous Elements

Twenty-two percent of SLCTs display heterologous elements, in the form of gastrointestinal-type mucinous epithelium, skeletal muscles, bone, cartilage, and other mesenchymal structures (Young and Scully 1985). Mucinous epithelium is the most common, constituting ~90 % of the heterologous differentiation (Fig. 19a). The average age is 24 years and androgenic symptoms are the main presentation. Apart from the associated heterologous elements, these tumors are morphologically similar to intermediately or poorly differentiated ones. Tumors with mucinous elements have a favorable outcome (Young et al. 1982). On the other hand, tumors with cartilage (Fig. 19b) and skeletal muscle elements have less favorable prognosis (Prat et al. 1982).

2.6.4 Differential Diagnosis

- Endometrioid and clear cell carcinomas. Clinical presentation in older age group, at least focal recognized areas of conventional carcinoma, positive EMA, and negative inhibin IHC stains favor carcinoma.
- Metastases. Bilaterality, signet rings and severe atypia favor a metastatic lesion.
- A wide variety of other possibilities, including other SCSTs, sarcomas, carcinosarcomas, teratomas (versus heterologous tumors), female adnexal tumor of probable Wolffian origin (FATWO), struma ovarii are worthy of consideration.

2.7 Sertoli Cell Tumors

2.7.1 Clinical Features

Less than 5 % of tumors with Sertoli component are pure Sertoli cell tumors (SCTs). The mean age of patients is 30 years. In contrast to SLCTs (see above), the pure ones are typically (~70 %) hormonally inert and minority of cases produce estrogen instead of androgen. Abdominal mass/swelling, pain, or menstrual irregularities are common presentations (Oliva et al. 2005).

2.7.2 Gross Pathology

As that with SLCT, SCTs are typically unilateral, solid, yellow tumors. Unlike SLCTs, cystic change is uncommon in SCTs. The average size is 9 cm (Oliva et al. 2005).

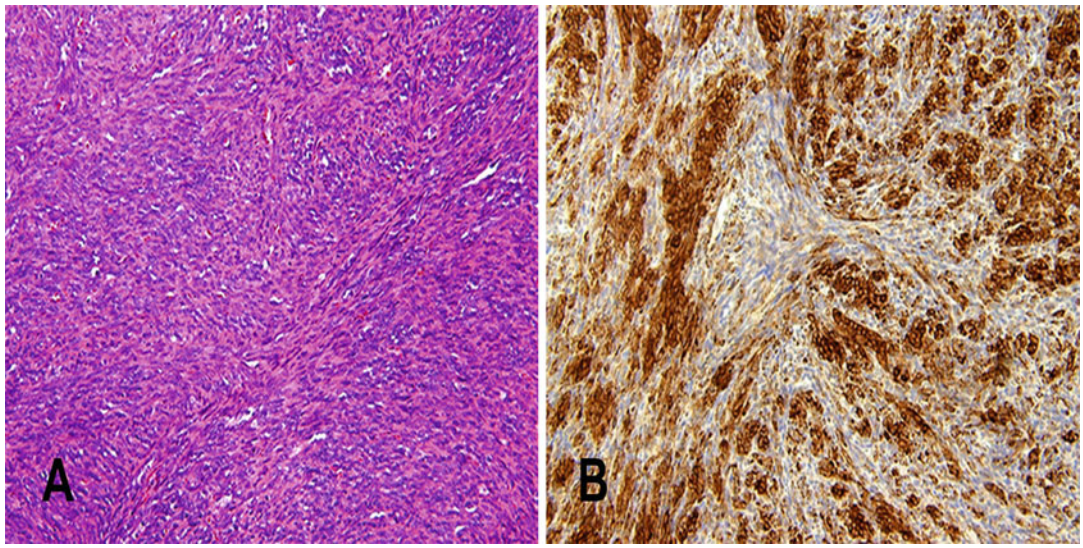

Fig. 18 Poorly differentiated Sertoli–Leydig cell tumor. (**a**) The tumor cells exhibit sarcomatoid growth pattern. They are formed of spindle cells mimicking sarcoma with high nuclear grade and absent tubule formation. (**b**) Inhibin stain by IHC is positive in tumor cells

2.7.3 Histopathology

SCTs composed of well-formed tubules in most cases. Other patterns, e.g., cord-like, trabecular, and diffuse could also be encountered. The glands are lined with cells with basally located round nuclei with grooves and moderate amounts of eosinophilic or lutenized cytoplasm. Mild cytologic atypia and few mitoses are the characteristic features in most cases. In cases with abundant lipid-rich cytoplasm, the term "lipid-rich" SCT is used. The background stroma is variable and occasionally sclerotic. As the case with SLCTs, these tumors are typically EMA and CK-7 negative and inhibin positive (Oliva et al. 2005).

2.7.4 Differential Diagnosis

- Sertoli cell tumor is differentiated from SLCT by the absence of Leydig cells in the former.
- Endometrioid carcinoma sometimes composed of closely packed tubules simulating Sertoli cell tumor. The older age, squamous differentiation, positive EMA, and negative inhibin support the diagnosis of carcinoma.
- Carcinoid tumors have characteristic morphology with "salt and pepper" chromatin, cytoplasmic granules, positive neuroendocrine markers, and negative inhibin.

2.8 Sex Cord–Stromal Tumors, Unclassified

A fraction (10–20 %) of SCSTs fall into this category. Clinical situation as pregnancy may cause difficulty in classifying SCSTs due to prominent edema, increased luteinization in GCTs, and prominent Leydig cells in SLCTs (Young et al. 1984b). Mixed patterns seen in different tumors as fibrothecomas, GCTs, and SLCTs may also qualify for the term unclassified (Seidman 1996).

2.9 Immunohistochemistry

The typical ovarian sex cord–stromal tumor is negative for EMA and is positive for calretinin, inhibin (Figs. 15 and 18), and to various extents, MART-1/melan-A, CD99, steroidogenic factor 1 (SF-1, adrenal 4-binding protein), WT1, and FOXL2 (Rabban and Zaloudek 2013) (Fig. 15). These markers have varying performances and some are more useful than the others for particular entities. However, a judiciously selected panel of markers can provide ample diagnostic information.

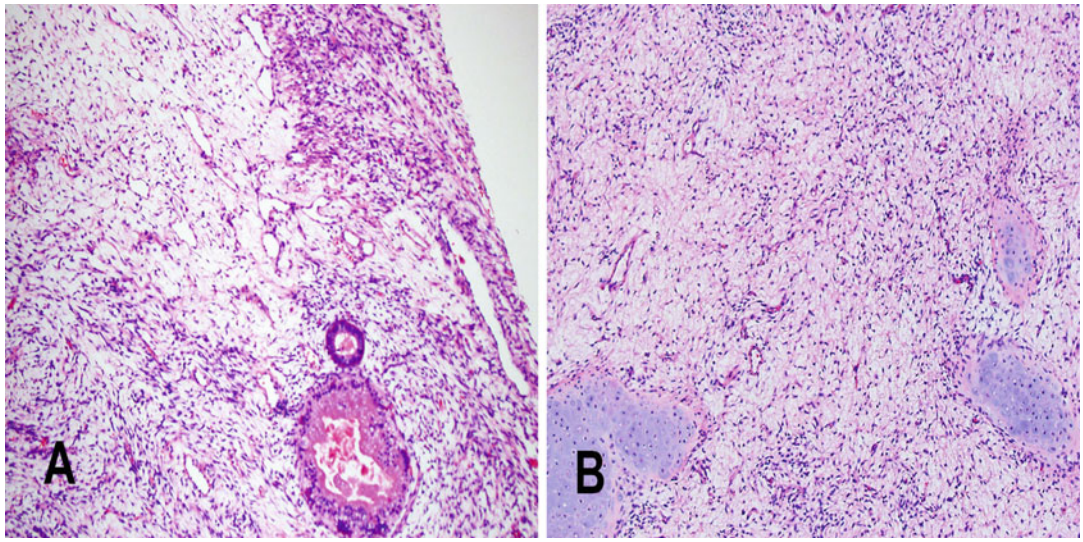

Fig. 19 Sertoli–Leydig cell tumor with heterologous elements. The tumor exhibits the morphology of intermediately differentiated tumor with alternating cellular and hypocellular stroma in lobulated pattern. Notice the presence of gastrointestinal mucinous elements in (**a**) and cartilaginous elements in (**b**)

3 Conclusion

In summary, ovarian SCSTs have a wide pathologic spectrum. Clinical information and morphologic and immunophenotypic profiles are important tools employed by the pathologist to accurately classify these tumors and to exclude differential diagnostic considerations that may be managed differently.

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Vaginal Hysterectomy: Indications, Avoiding Complications

Begüm Özel

Abstract

Vaginal hysterectomy is believed to have been first successfully performed in 1813. Most women requiring a hysterectomy are candidates for the vaginal approach, and it should always be considered as first-line approach to hysterectomy. Both the American Congress of Obstetrics and Gynecology and the American Academy of Gynecologic Laparoscopists recommended vaginal hysterectomy whenever possible. Previous cesarean delivery and obesity are not contraindications to the vaginal approach; in fact the vaginal approach may be preferred in these patients. Paracervical vasopressin has been shown to decrease blood loss during vaginal hysterectomy, although the difference may not be clinically significant. Preemptive oral gabapentin and preemptive local anesthesia reduce post-op pain. Vaginal salpingoo-phorectomy and salpingectomy can be accomplished in the majority of patients. Unless vaginal apical suspension is planned, a modified McCall-type culdoplasty should be performed to prevent enterocele formation and to reattach the uterosacral ligaments to the vaginal cuff. In randomized trials, women returned to normal activities sooner after vaginal compared to abdominal hysterectomy and have less wound infections, urinary tract infections, and febrile episodes after a vaginal versus abdominal hysterectomy. Compared to laparoscopic-assisted vaginal hysterectomy or total laparoscopic hysterectomy, vaginal hysterectomy has shorter operating time, hospital stay, and cost. Complications occur in about 5% of cases, with the most common complications being cuff infection/abscess and dissection cystotomy. Cuff infection/abscess complicates about 1.2% of case, while dissection cystotomy occurs in roughly 0.5% of cases. Ureteral injury is relatively rare, but pelvic organ prolapse increases the risk of this complication.

Keywords

Hysterectomy • Vaginal • Laparoscopic • Cost • Complications • Vaginal hysterectomy

Contents

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1 Background

The first report of a vaginal hysterectomy was for a gangrenous prolapsed uterus, reported by Soranus of Ephesus in 120 AD; however, it involved transection of the bladder and ureters (Sutton 2010). A second well-documented case was of Faith Howard, a peasant woman who grew tired of her prolapsed uterus and amputated it with a sharp knife; unfortunately she also suffered subsequently from "water passing from her insensible day and night" (Sutton 1997). In 1813, Conrad Lagenbeck of Gottingen performed the first planned and successful surgical vaginal hysterectomy (Sutton 1997).

Today hysterectomy is one of the most commonly performed surgical procedures. Roughly 600,000 hysterectomies are performed annually in the United States. Both the American Congress of Obstetricians and Gynecologists the American Association of Gynecologic Laparoscopists recommend vaginal hysterectomy as the preferred route of hysterectomy for benign indications (ACOG 2009; AAGL 2011). Despite this, there has been a decline in the percentage of hysterectomies performed vaginally in the United States, from 24.8% in 1998 to 16.9% in 2012 (Desai 2015).

A major challenge to vaginal hysterectomy is inadequate training. In a recent survey of fellowship program directors, only 20% of graduating obstetrics and gynecology residents starting fellowship in female pelvic medicine and reconstructive surgery were deemed competent to independently perform a vaginal hysterectomy (Guntupalli et al. 2015). In 2010, a survey of graduating residents found that one third felt unprepared to perform a vaginal hysterectomy independently, and only 27.8% of graduating residents reported being "completely prepared." In comparison, only 5.6% and 19.5% of graduating residents felt unprepared to independently perform abdominal hysterectomies and laparoscopic hysterectomies, respectively (Burkett et al. 2011). In another survey of graduating senior resident, 90% stated that they would perform vaginal hysterectomy in the future and 75% felt adequately trained. Residents were more likely to feel comfortable performing the procedure independently if they had performed more than 20 vaginal hysterectomies (odds ratio [OR], 10.2; 95% CI, 3.3–30.9; $P < 0.0001$) and if they learned vaginal morcellation techniques (OR, 5.1; 95% CI, 1.5–17.8; $P = 0.01$) (Antosh et al. 2011).

There has been a decrease in the number of vaginal hysterectomies performed by residents during training, despite no change in the total number of hysterectomies being performed over the 4-year residency training. The mean number of hysterectomies performed by residents was 118.1 cases in 2008–2009 and 116.1 cases in 2011–2012 ($p = 0.16$); however, the number of vaginal hysterectomies performed went from 34.9 cases to 19.4 cases during the same time period, representing a 40% decrease ($p < 0.001$; 95% CI, 14.3–16.7) (Washburn et al. 2014).

One reason behind this is believed to be an increase in laparoscopic and robotic hysterectomies. Between 2007 and 2010, the rate of robotic hysterectomy increased from 0.5% to 9.5%, and the rate of laparoscopic hysterectomy increased from 24.3 to 30.5% in 441 hospitals in the United States (Wright et al. 2013b). In another study of 1440 hysterectomies performed at four academic medical centers, the proportion of hysterectomies performed via the vaginal route decreased from 42.5% before the introduction of the robot to the medical centers to 30.5% after the robot ($p < 0.0001$) (Jeppson et al. 2015).

The vaginal hysterectomy remains the most minimally invasive technique for the surgical removal of the uterus, with the advantage of quickest recovery, lowest complications, and best cosmesis. It is also the most cost effective among the various approaches to hysterectomy with an average cost savings of $2200 per hysterectomy (Woelk et al. 2014). Total laparoscopic hysterectomy costs on average $3500 more per case and robotic hysterectomy more than $5000 more per case than vaginal hysterectomy (Dayaratna et al. 2014).

2 Indications and Patient Selection

Most common benign indications for hysterectomy are leiomyoma, abnormal uterine bleeding, endometriosis, benign ovarian neoplasm, and pelvic organ prolapse (Wright et al. 2013a). The most common indication for a vaginal hysterectomy is uterine prolapse, which in 2005 accounted for 62% of cases (Clarke-Pearson and Geller 2013). With appropriate patient selection, vaginal hysterectomy can be performed for any benign indication.

Kovac described guidelines to determine if a patient was a vaginal hysterectomy candidate and applied them in a resident clinic (Fig. 1) (Kovac et al. 2002). The first determination is whether the uterus is accessible vaginally. This determination was made with the following criteria: the uterus is deemed accessible transvaginally if the vagina is >2 fingerbreadths in width at the apex or if the uterus is at least stage 1 when the Valsalva maneuver is performed. If there was adequate vaginal access, then uterine size was taken into consideration. If the uterus was estimated to be less than 12 weeks or 280 gm, then a vaginal approach was appropriate. Although other formulas exist, the simplest and easiest to remember formula to estimate uterine weight is $0.52 \times \text{length} \times \text{width} \times \text{depth}$ based on ultrasound measurements (Goldstein et al. 1988). If the clinical history or pelvic examination indicated possible extrauterine disease (endometriosis, pelvic inflammatory disease, ovarian disease, or chronic pelvic pain), laparoscopic assistance was performed to confirm the presence and the extent of extrauterine pathologic condition accurately and whether operative laparoscopy would permit vaginal hysterectomy to be performed. Consideration was also given to the appropriateness and ability to perform uterine size reduction techniques, such as morcellation, myomectomy, or coring. Using these criteria, 92% of planned vaginal hysterectomies could be accomplished vaginally in a resident clinic population (Kovac et al. 2002). There were no conversions from vaginal hysterectomy to abdominal hysterectomy due to findings on laparoscopy; the remainder of the cases was performed abdominally or with laparoscopic assistance.

Vaginal hysterectomy may be appropriate in women with uterus >12 weeks without an increased rate of complications (Cho et al. 2014; Fantania et al. 2014; Sahin 2007). However, mean operating time was significantly longer in the uteri ≥280 gm than in the <280 gm (69.4 ± 24.4 versus 108.2 ± 41.2 min, $p < 0.0001$). There was also a higher rate of hemorrhage as defined as a fall in hemoglobin value of >4 g/100 mL. (8.43% versus 1.2%) in women with uteri ≥280 gm (Sahin 2007).

Although there is some data suggesting that women with two or more prior cesarean deliveries may be at higher risk of bladder injury with a vaginal hysterectomy (Duong and Patterson 2014), prior cesarean delivery does not contraindicate a vaginal hysterectomy (Purohit et al. 2013; Unger and Meeks 1998), and a history cesarean delivery is known to be a risk factor for bladder injury regardless of the route of hysterectomy (Rooney et al. 2005).

Obesity is not a contraindication, and vaginal hysterectomy remains the procedure of choice in obese women who are having a hysterectomy (Harmanli et al. 2011; Muffly and Kow 2014; Sheth 2010).

3 Contraindications

There are contraindications to a vaginal hysterectomy which include cervical cancer, endometrial hyperplasia, or malignancy when morcellation

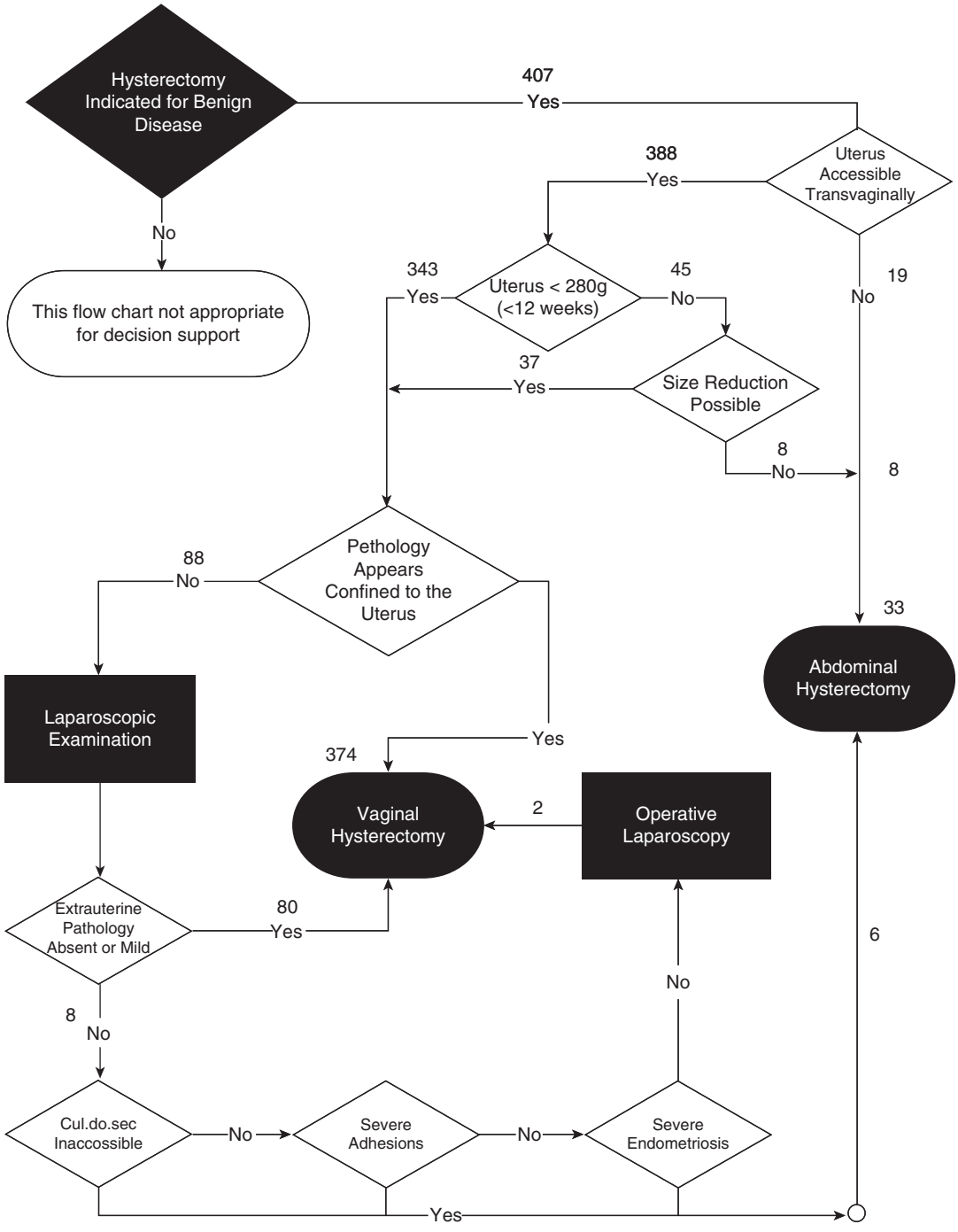

Fig. 1 Determining the route of hysterectomy (Reprinted from Kovac et al. (2002), with permission from Elsevier)

would be necessary; concern for leiomyosarcoma when morcellation would be necessary; large ovarian mass, especially when there is concern for malignancy; and large cervical leiomyoma when the uterine vessels cannot be accessed. Severe pelvic adhesions, obliterated cul-de-sac,

and very large uterine size are all relative contraindications.

4 Technique

4.1 Vaginal Prep

Vaginal preparation with povidone iodine or chlorhexidine solution is routinely performed to decrease infectious morbidity. Use of saline to prep the vaginal has been shown to increase infectious morbidity in the early post-op period (Kjolhede et al. 2011). Culligan and colleagues found that 4% chlorhexidine gluconate with 4% isopropyl alcohol was more effective than povidone iodine in decreasing the bacterial colony counts that were found in the operative field for vaginal hysterectomy (Culligan et al. 2005).

4.2 Antimicrobial Prophylaxis

It is standard of care to provide perioperative antimicrobial prophylaxis in all hysterectomy cases. First-generation cephalosporins, such as cefazolin, are as effective as second- or third-generation cephalosporins and are less expensive. They are also less likely to induce bacterial beta-lactamase response. In women who are penicillin allergic, alternatives include clindamycin or metronidazole plus a fluoroquinolone (ciprofloxacin or levofloxacin) or gentamicin. Repeat dosing is recommended after 3 h of when estimated blood loss is greater than 1500 ml. Antibiotics should not be continued past 24 h postoperatively.

4.3 Patient Positioning

Optimal position will result in both excellent exposure and minimize the risk of patient injury. The patient is positioned in high dorsal lithotomy in boot-type or candy cane stirrups. It is important to avoid hyperflexion or external rotation of the hips to prevent stretch injury to the sciatic nerve and compression injury to the femoral nerve which passes under the ilioinguinal ligament in the groin. It is important to place the legs in the position that they will be in during the case before draping to ensure that there is no hyperflexion at the hip when the legs are raised to high lithotomy. The peroneal nerve is also at risk during lithotomy, and care should be made to prevent bowing out of the knee which can cause stretch injury during the use of candy cane stirrups. The nerve can also be subject to compression injury with boot-type stirrups. Extra padding should be used if needed. The posterior tibial nerve is stretched with ankle dorsiflexion and can also be at risk when the foot is in candy cane stirrups. Consideration should be given to positioning the patient in stirrups when she is awake if she has any issues with pain or limiting mobility of her lower extremities.

It is helpful to use a foam egg crate on the table and place the patient directly on the foam egg crate to minimize sliding up on the bed with Trendelenburg. The patient should be placed in Trendelenburg at the start of the case to allow for visualization and to move small bowel out of the cul-de-sac. The patient should be positioned on the operating table so that her buttocks are over the edge of the cutout in the table. This will help when retractors are used.

4.4 Vasopressin

A dilute vasopressin solution may be injected paracervically to reduce blood loss during vaginal hysterectomy. When vasopressin is injected into tissue, it has a vasoconstrictive effect that is produced by the contraction of smooth muscle cells in vessels. This effect lasts less than an hour and the half-life is 10–20 min. Kammerer-Doak and colleagues conducted a randomized controlled trial of 117 women who received paracervical vasopressin versus saline during vaginal hysterectomy; 8 mL of vasopressin (20 units/100 mL normal saline solution) is injected into the submucosa circumferentially around the cervix in six small wheals at the 1, 3, 5, 7, 9, and 11 o'clock positions (Kammerer-Doak et al. 2001). They found that estimated blood loss (312 ± 222 mL vs. 446 ± 296 mL; $p = 0.006$) and change in

hemoglobin and hematocrit levels (2.1 ± 1.4 gm vs. 2.9 ± 1.4 gm; $p = 0.02$; and 6.7% ± 3.4% vs. 8.5% ± 3.8%; $p = 0.01$; vasopressin versus normal saline solution, respectively) were significantly less in the vasopressin group. There was no significant difference in infection rates; in fact, the normal saline solution group had a higher rate of infection (7.3%) compared with the vasopressin group (1.6%; relative risk, 4.51; 95% CI, 0.52–39.14; $p = 0.19$). In another randomized controlled trial, 20 mL (8 units) of dilute vasopressin solution (20 units of vasopressin in 50 mL of normal saline) was injected in 5 mL increments at 2, 4, 8, and 10 o'clock circumferentially around the cervix at the cervicovaginal junction. The use of vasopressin injected paracervically resulted in significantly less blood loss (145.3 mL compared with 266.4 mL control; $p = 0.022$). However, there was no difference in postoperative hematocrit, but there was a significant difference in the increase in mean blood pressure at 5 min after injection (10.4 for the vasopressin group compared with 2.5 for the control group, $p = 0.043$) as well as an increase in patient-controlled anesthesia usage postoperatively (Ascher-Walsh et al. 2009).

5 Preemptive Techniques to Minimize Postoperative Pain

Gabapentin is a gamma-aminobutyric acid (GABA) analogue that has been shown to be effective in the treatment of neuropathic pain; its use has been studied perioperatively to decrease post-op pain and requirements. The mechanism of action is unknown since it does not appear to interact with GABA receptors. Rorarius and colleagues performed a double-blind randomized study of 1200 mg of gabapentin versus 15 mg of oxazepam 2.5 h before surgery in women undergoing elective vaginal hysterectomy (Rorarius et al. 2004). They found that women treated with gabapentin needed approximately 40% less doses of fentanyl than women in the control group. The women who received gabapentin also had significantly less nausea. There were no differences in medication related side effects.

The use of preemptive local anesthesia in vaginal hysterectomy may be beneficial in terms of postoperative pain. O'Neal and colleagues conducted a small randomized controlled trail of 20 women; one group received paracervical injection of 0.5% bupivacaine with epinephrine, while the other group received saline injections (O'Neal et al. 2003). Pain scores were lower in the bupivacaine group ($p = 0.03$). Total morphine and patient-controlled analgesia morphine was significantly less in patients receiving bupivacaine ($p = 0.01$ and 0.04). There was no difference in estimated blood loss or length of hospital stay. Long and colleagues compared paracervical injection of 20 mL of 0.5% bupivacaine with 1:200,000 epinephrine to placebo in a randomized controlled trial of 90 women having a vaginal hysterectomy and found that the mean total dose of narcotic within the first 24 h was 30% lower for the bupivacaine group than the placebo group ($p = 0.009$), and pain on the visual analogue scale was significantly lower at 30 min and 3 h postoperatively with no difference at 12 and 24 h (Long et al. 2009).

A randomized controlled trial using ropivacaine in a modified paracervical block before prior to incision found that this significantly reduced both pain at rest up to 8 h and pain with coughing and movement up to 4 h after surgery (Hristovska et al. 2014). The median time until first ambulation was significantly shorter in the ropivacaine group, and the use of post-op analgesics was significantly less in the ropivacaine group. In this study ropivacaine 0.50% or saline 30 mL was injected before incision as a modified paracervical block; 5 mL was injected through the vaginal fornices at 2, 4, 6, 8, 10, and 12 o'clock at 2 cm depth while the needle was retracted, and 2 mL was injected in each resection line (uterosacral and cardinal ligaments and the adnexal corners) close to the suture.

5.1 Surgical Steps

The bladder is initially drained, and a Foley catheter is left in place but clamped during the case. This allows for intermittent bladder drainage, as

well as allowing the surgeon to palpate the Foley balloon to identify the bladder. Lastly, since the bladder is not continuously drained, an incidental cystotomy should be easy to identify because of the drainage of urine through the cystotomy site.

A weighted speculum is placed in the vagina. A Heaney retractor can be used to retract the anterior vaginal wall to visualize the cervix. The cervix is grasped with a double tooth Jacobs' tenaculum or Lahey clamp. Traction and counter traction throughout the case are important to increase the distance between the clamps and the ureters.

An incision is made in the full thickness of the vagina around the cervix either with cautery or with a knife. This incision should be made just at the point that the vaginal rugae appear anteriorly and laterally and a few millimeters proximal to this point posteriorly. The posterior peritoneal reflection is then identified and grasped with tissue forceps and entered sharply with curved Mayo scissors. At this point, either a Heaney retractor or a long weighted speculum can be inserted though the posterior colpotomy.

The bladder is then dissected off the anterior cervix with Metzenbaum scissors (Fig. 2). The anterior peritoneal reflection appears as a smooth crescent-shaped line above the level of the cervix. The Foley balloon can aid in identifying the bladder during dissection. If entry is difficult, if the uterus is small enough, a finger can be placed over the uterine fundus and the anterior peritoneal reflection palpated and identified. Otherwise, the bladder can be dissected off the cervix anteriorly, and so long as it is off the cervix, ligation of the pedicles can occur. With the resulting uterine descent, the anterior peritoneal reflection will become easier to identify. It is important not to rush to try to enter anteriorly without good visualization. Once the anterior peritoneum is entered, a Heaney or Deaver retractor can be placed into this space.

The uterosacral ligaments are then clamped, transected, and suture ligated bilaterally. The clamp is placed perpendicular to the cervix and the tissue is cut so as to leave a small amount of tissue distal to the clamp. A Heaney needle driver is useful during a vaginal hysterectomy for suturing in tight spaces. It is best to ligate this pedicle with a Heaney stitch because this pedicle will be tagged with a Kelly clamp or hemostat to help with visualization of the pedicles at the end of the case. If it is not transfixed, the suture can easily slip off.

The cardinal ligaments are then clamped, transected, and suture ligated bilaterally. When the cervix is long, it will take several bits of tissue to fully ligate this ligament. The uterine arteries are clamped, transected, and suture ligated on both sides. Again, traction and counter traction are important at this point to increase the distance between the arteries and the ureters. The anterior peritoneal reflection should be entered if it has not been entered yet.

The broad ligament is then clamped. At this point it is important not to place too much traction on the uterus since the primary support structures have been transected, and there is a risk for avulsion of the upper pedicles. The triple pedicle (round ligament, fallopian tube, utero-ovarian ligament) can be tied off with a free tie, which is held to allow for identification of this pedicle before closing, and then clamped, transected, and suture ligated.

Once the uterine arteries are ligated, it is possible to start using techniques to facilitate removal of an enlarged uterus. However, these techniques should be avoided if there is any risk for malignancy. These techniques include bivalving, which can be accompanied by morcellation, or coring of the myometrium. The latter is accomplished by circumferentially incising the myometrium

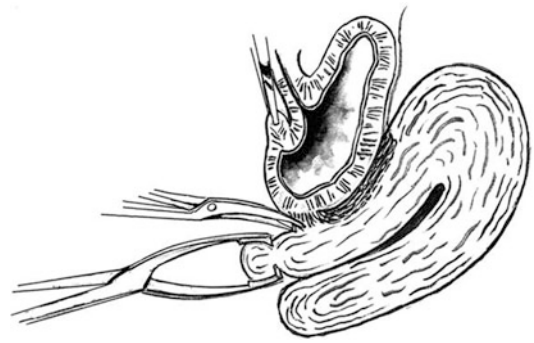

Fig. 2 Dissection of the bladder off the anterior cervix and uterus (Reprinted from Unger and Meeks (1998), with permission from Elsevier)

beneath the serosa with a scalpel while placing the cervix on tension. This allows for delivery of the uterus in one elongated piece.

A sponge stick or moist vaginal pack can be placed in the peritoneal cavity to retract bowel and allow for visualization of the pedicles. At this point there should be a tag on both the first and last pedicles so that the entre suture line can be visualized on both sides. If there is good hemostasis, the free tie on the triple pedicle can be cut. It is important to note that only the free tie should be tagged and not the ligated stitch since the traction on the stitch may cause it to come lose resulting in loss of this pedicle which can be hard to reidentify vaginally. There is little harm to the free tie coming lose because it is not a hemostatic tie.

Salpingectomy, salpingo-oophorectomy, culdoplasty, or apical suspension can be performed next. The cuff is closed with continuous locked or interrupted figure of eight stitches. The culdoplasty stitch is tied last.

5.2 Energy-Based Sealing Devices

Energy-based sealing devices are an alternative to using suture ligation for vaginal hysterectomy. In a meta-analysis, energy-based vessel-sealing devices decreased operative time by a mean of 17.2 min (seven studies, 662 patients; 95% confidence interval [CI] 7.5–27.0), blood loss by a mean of 47.7 mL (five studies, 437 patients; 95% CI 15.5–79.9), drop in hemoglobin by 0.3 g/dL (two studies, 291 patients; 95% CI 0.1–0.6), and postoperative hospital stay by 0.25 days (five studies, 554 patients; 95% CI 0.13–0.37). There was no increase in the rate of complications for energy-based vessel sealing compared with traditional suturing (Kroft and Selk 2011).

Two studies were published since that meta-analysis which both showed reduced operating time with the use of energy-based sealing devices. In a randomized study comparing using Ligasure™ Impact (LF4200) in combination with the ForceTriad™ energy platform (Covidien; Tyco Healthcare, Valleylab, CO, USA) to traditional suture ligation in 100 women, operating time was shorter in the vessel-sealing group (59.7 versus 71.3 min, $p = 0.05$); the amount of blood loss and duration of hospital stay did not differ (Lakeman et al. 2012). Pain scores after surgery were significantly different on the evening after surgery (5.7 versus 4.5 on a scale of 0–10 for Ligasure versus traditional suture, respectively, $p = 0.03$) but were similar thereafter. Silva-Filho and colleagues compared the bipolar vessel-sealing system (Ligasure, Valleylab, Boulder, CO) with conventional suturing in a randomized trial of 90 women having a vaginal hysterectomy (Silva-Filho et al. 2009). They also found reduced operating time (29.2 $\pm$ 2.1 min vs. 75.2 $\pm$ 5 min; $p < 0.001$), as well as reduced operative blood loss (84 $\pm$ 5.9 mL vs. 136.4 $\pm$ 89.1 mL; $p = 0.001$), pain at 12 h after surgery (1.6 $\pm$ 0.4 vs. 3.6 $\pm$ 0.4; $p < 0.001$) and hospital stay (25.6 $\pm$ 0.9 h vs. 33.2 $\pm$ 1.7 h; $p < 0.001$) compared to the control group. There was no increase in complications.

The Harmonic scalpel (Ethicon Endo-Surgery, Inc., Cincinnati, OH) was compared to traditional suture ligation in a randomized trial of 40 women and was found to result in no difference in operative time, clinically significant blood loss, or analgesic requirements (Fitz-Gerald et al. 2013). Estimated blood loss was significantly less in the Harmonic scalpel group [62.63 (12.46) mL vs. 136.05 (21.54) mL; $p = 0.006$], but this did not translate into any significant differences in change in hemoglobin levels after surgery.

5.3 Vaginal Salpingo-Oophorectomy

Planned oophorectomy and/or salpingectomy do not contraindicate vaginal approach to the hysterectomy. The uterus is typically removed first, and the adnexa are then examined. It is helpful to grasp the ovary and tube with a Babcock clamp and gently pull the adnexa into the operative field to determine if the infundibulopelvic ligament can be accessed. Sometimes packing the bowel up with a moist pack can be helpful. A peon clamp can then be placed across the infundibulopelvic ligament; it is important to note that once the

clamp has been placed, it should not be removed and one is committed to the salpingo-oophorectomy because removal of the clamp may result in bleeding from the vessels and retroperitoneal hematoma formation. A peon clamp is preferred because it is less traumatic. The adnexa are then transected with scissors and the pedicle ligated with a Heaney stitch using 0 delayed absorbable suture. It is not necessary or advisable to try to place a free tie around this pedicle as it may result in losing the pedicle. Vaginal salpingectomy can be accomplished in a similar manner by grasping with a Babcock clamp, placing a peon clamp across the mesosalpinx, transecting the tube, and ligating the pedicle with 0 delayed absorbable suture.

Karp and colleagues found that 65% of adnexa can be safely removed vaginally, and younger age (OR = 2.18, CI 1.1–8.4, $p < 0.001$) and shorter cervical length (OR = 4.5, CI 1.2–10.7, $p < 0.001$) were predictors of success (Karp et al. 2012). Dain also reported that younger age was associated with greater likelihood of success of vaginal salpingo-oophorectomy (Dain and Abramov 2011). Vaginal salpingectomy is possible in 65–88% of cases (Dain and Abramov 2011; Karp et al. 2012; Robert et al. 2015). However, in cases were removal of the adnexa is absolutely necessary, such as in women with complex endometrial hyperplasia or BRCA mutation, it is advisable to consider adding laparoscopic for removal of the adnexa; this will also allow for survey of the pelvis and obtaining pelvic washings in these high-risk individuals.

5.4 Culdoplasty

In the absence of other procedures to suspend the vaginal apex, such as an uterosacral or sacrospinous colpopexy, a culdoplasty is generally recommended at the time of vaginal hysterectomy to prevent formation of an enterocele and vaginal vault prolapse (Fig. 3). Cruikshank and Kovac demonstrated that a modified McCall-type culdoplasty is best at preventing enterocele after vaginal hysterectomy (Cruikshank and Kovac 1999). The modified McCall's culdoplasty not only closes the cul-de-sac to prevent an enterocele, it reattaches the transected uterosacral ligaments to the vaginal apex, thereby providing apical support to the vagina.

5.5 Cuff Closure

Two randomized studies suggest that vertical cuff closure appears to preserve vaginal length better than horizontal cuff closure. Vassallo and colleagues found in their randomized trial of 43 women that closing the cuff vertically resulted in lesser mean change in vaginal length

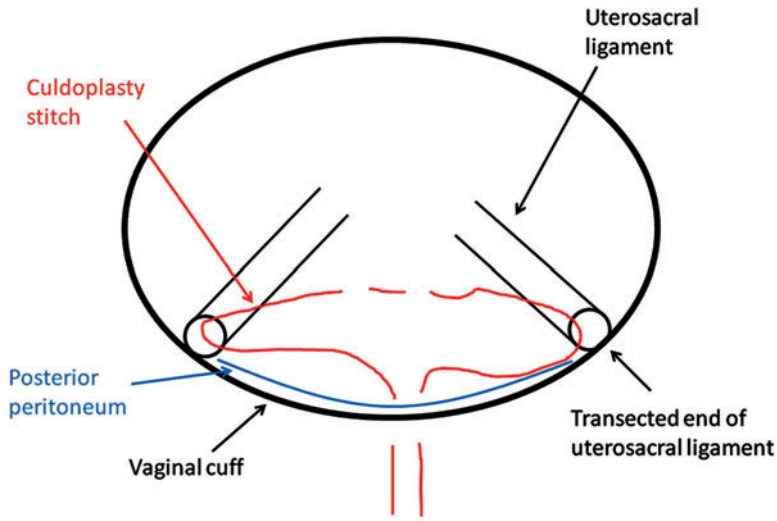

Fig. 3 Modified McCall culdoplasty

(−0.35 +/− 0.91 cm) compared to horizontal closure (−1.13 +/− 1.15 cm) ($p = 0.01$) (Vassallo et al. 2006). In another randomized trial of 52 women without pelvic organ prolapse having a vaginal hysterectomy, at 6 weeks postoperatively, the vagina was significantly shorter in the horizontal closure group (6.55 [0.89] cm vs. 7.42 (0.73) cm; $p < 0.001$) (Cavkaytar et al. 2014). However, Cruikshank and Pixley compared five different cuff closure techniques in 107 women and found no difference in vaginal length (Cruikshank and Pixley 1987). The clinical significance of this remains unclear.

The use of vault drainage has been examined in a randomized trial and found to offer no benefit (Dua et al. 2012). Likewise, peritoneal closure does not appear to be necessary (Lipscomb et al. 1996).

5.6 Post-op Care

Vaginal hysterectomy can be performed on an outpatient basis. Summitt and colleagues in 1992 demonstrated that the majority of women can be discharged home within 12 h of surgery once ambulating, voiding, and tolerating a liquid diet (Summitt et al. 1992). In a more recent study, 84% of healthy (ASA I or II) women after a mean observation period of 4.6 h were discharged home post-op day 0 (Engh and Hauso 2012).

Postoperative catheterization is not mandatory but short-term catheterization is probably without significant risk. Ideally the urinary catheter should be removed within 24 h after surgery. Summitt and colleagues randomized 100 women having vaginal hysterectomy to no catheter after surgery versus catheterization for 24 h after surgery (Summitt et al. 1994). Two (4%) of women without a catheter required catheterization after surgery. They found no difference in post-op febrile episodes or urinary tract infections. Also no differences were found in the incidence of positive urine cultures between the study groups at 48 h (8 vs. 14, $p = 0.227$) and 2 weeks (6 vs. 1, $p = 0.111$), respectively.

5.7 Outcomes Compared to Other Types of Hysterectomy

The American Congress of Obstetrics and Gynecology and the American Academy of Gynecologic Laparoscopists have both recommended vaginal hysterectomy whenever possible as the best route of hysterectomy.

> Recent Cochrane meta-analysis (Aarts et al. 2015) demonstrated that for women undergoing hysterectomy for benign disease, vaginal hysterectomy appears to be superior to both abdominal and laparoscopic hysterectomy and is associated with faster return to normal activities.

In this meta-analysis, 47 randomized controlled trials including 5102 women were reviewed. The majority of these studies excluded women with pelvic organ prolapse or with uterus >12–16 weeks. The Cochrane review included nine trials with 762 women comparing vaginal versus abdominal hysterectomy. Women returned to normal activities sooner after vaginal hysterectomy compared to abdominal hysterectomy (Median difference 9.5 days, 95% CI 6.4 to 12.6 days; 176 women, three trials). More women would choose a vaginal hysterectomy again when compared to an abdominal hysterectomy. There were three times as many urinary tract injuries after vaginal versus abdominal hysterectomy, although there was no statistical difference (OR 3.09, 95% CI 0.48 to 19.97, four RCTs, 439 women) (Aarts et al. 2015). There was no difference in other intraoperative complications or operative time. Hospital stay was shorter in vaginal hysterectomy compared to standard abdominal hysterectomy. Wound/abdominal wall infection (OR 0.21, 95% CI 0.04 to 1.00, three RCTs, 355 women), urinary tract infection (OR 0.59, 95% CI 0.08 to 4.61, three RCTs, 176 women), and febrile episodes or unspecified infections (OR 0.62, 95% CI 0.36 to 1.08, five RCTs, 495 women) all occurred less after VH than after AH, but there was no statistical difference.

The Cochrane group also reviewed 16 studies including 1440 women comparing vaginal hysterectomy to laparoscopic hysterectomy (including both laparoscopic-assisted vaginal hysterectomy and total laparoscopic hysterectomy). No advantage of laparoscopic-assisted vaginal hysterectomy or total laparoscopic hysterectomy over vaginal hysterectomy was demonstrated (Aarts et al. 2015). Hospital stay was 1 day shorter after vaginal hysterectomy. Women undergoing laparoscopic hysterectomy returned to work 1 day earlier than women undergoing VH, but the time to return to normal activities showed no evidence of a difference. There was no statistical difference in intraoperative or postoperative complications. Operating time is longer with a laparoscopic approach compared to vaginal hysterectomy. Although one study demonstrated lower post-op pain with laparoscopic hysterectomy (Ghezzi et al. 2010), other studies have not found similar results. Cost analysis has shown that mean total hospital charge when surgery was performed on an outpatient basis was significantly higher for laparoscopic hysterectomy compared to vaginal hysterectomy (Summit et al. 1992).

The eVALuate study was a major multicenter study that consisted of two parallel randomized trials – one that compared abdominal hysterectomy to total laparoscopic hysterectomy and the other compared vaginal hysterectomy and total laparoscopic hysterectomy (Garry et al. 2004). Included in the study were women who needed a hysterectomy for nonmalignant conditions, and excluded were those who had a second or third degree uterine prolapse, a uterine size greater than the size of a 12-week pregnancy, a medical illness precluding laparoscopic surgery, or a requirement for bladder or other pelvic support surgery. It is the largest study to date comparing vaginal and total laparoscopic hysterectomy; 504 women were enrolled in the vaginal trial. There was no difference between vaginal and total laparoscopic hysterectomy in terms of complications, pain, and length of stay. Vaginal hysterectomy had a significantly shorter operating time (46.6 versus 76.5 min for vaginal versus laparoscopic, respectively).

While most randomized trials included women with only a slightly enlarged uterus, less than 12 weeks, Sesti and colleagues conducted a randomized study of women having a hysterectomy for benign reasons with a uterus between 12 and 16 weeks in size (Sesti et al. 2014). Women were randomized to vaginal hysterectomy, laparoscopic-assisted vaginal hysterectomy, or total laparoscopic hysterectomy; there were 36 women in each group. All surgeons were experienced in all three techniques, having performed at least 100 of each type of hysterectomy. Operating time (mean 70 min) and estimated blood loss (mean 182.8 mL) was significantly less in the vaginal hysterectomy group compared to both laparoscopic-assisted vaginal hysterectomy and total laparoscopic hysterectomy. The mean hospital discharge time was also significantly shorter after VH (50.7 h). There were no differences in complication rates.

In another study of hysterectomies for enlarged uterine size >280 g with at least one additional risk factor, previous pelvic surgery, history of pelvic inflammatory disease, moderate or severe endometriosis, concomitant adnexal masses, or indication for adnexectomy, Darai and colleagues randomized 80 women to laparoscopic-assisted vaginal hysterectomy versus vaginal hysterectomy (Darai et al. 2001). They found lower rate of complications with vaginal hysterectomy (15% with vaginal hysterectomy versus 37% with laparoscopic-assisted vaginal hysterectomy, $p < 0.05$) and shorter operating time with vaginal hysterectomy [mean operating time (range) was 108 (60–270 min) min for vaginal hysterectomy and 160 min (60–180 min) for laparoscopic-assisted vaginal hysterectomy ($p < 0.001$)]. Conversion to laparotomy was required in 3 of 40 (7.5%) women who had laparoscopic-assisted vaginal hysterectomy, compared with none in the vaginal hysterectomy group ($p < 0.05$). No difference was found in the mean uterine weight (range) between vaginal hysterectomy and LAVH groups [424 g (280–930) and 513 g (290–1560), respectively]. The study included 13 cases (32.5%) of uterine size at least 500 gm in the vaginal hysterectomy group that were successfully completed vaginally.

Wright and colleagues looked at actual patient charges for the various modes of hysterectomy and found that at their institution, Brigham and Women's Hospital, women who had a vaginal hysterectomy had the shortest operating time [mean 153 min (95% confidence interval 143.8–163.5, $p < 0.001$)] and women who had a vaginal, laparoscopic, and robotic hysterectomy had a significantly shorter hospital stay compared to those who had an abdominal hysterectomy. The mean length of stay for vaginal hysterectomy was 1.24 days. Based on this they calculated mean total patient costs and found that it was significantly lower for vaginal hysterectomy compared to other modes of hysterectomy (Wright et al. 2012); the mean cost for vaginal hysterectomy was $31,934, whereas robotic hysterectomy, the most expensive of the four modes of hysterectomy, costs $49,526.

5.8 Complications

Vaginal hysterectomy is associated with complications in 5.2% of women (Makinen et al. 2013). The most common complications are cuff cellulitis and abscess and incidental cystotomy. Surgical site infections are reported in 12 per 1000 women (Roy et al. 2014).The rate of cuff cellulitis is 0.6%, and the rate of deep/organ space surgical site infection is 1.0% after a vaginal hysterectomy (Lake et al. 2013). Bladder and ureteric injury are reported to occur at a rate of 5.1 per 1000 women and 0.4 per 1000 women, respectively (Teeluckdharry et al. 2015). In one large retrospective study where universal cystoscopy was used, the authors found that the rate of ureteral injury is higher when there is concomitant prolapse repair (0.9% versus 1.7%) (Ibeanu et al. 2009). The use of routine cystoscopy has been suggested to be cost effective if the rate of ureteral injury is greater than 2% for vaginal hysterectomy (Visco et al. 2001). The risk of vesicovaginal fistula formation is the lowest after vaginal hysterectomy for prolapse with a rate of 1 in 3861 or 0.26 per 1000 (Hilton and Cromwell 2012). The rate of bowel injury during vaginal hysterectomy ranges from 0.1% to 1.0% (Clarke-Pearson and Geller 2013). The estimated blood loss for a vaginal hysterectomy is 215–287 mL (Clarke-Pearson and Geller 2013). Urinary tract infection is reported in 3.1% of cases (Lake et al. 2013). Vaginal cuff dehiscence is lowest after vaginal hysterectomy compared to other routes of hysterectomy and is reported in 0.11% of cases (Hur et al. 2011). Pulmonary complications, defined as postoperative pneumonia, respiratory failure, symptomatic atelectasis (requirement of intervention, such as bronchoscopy, respiratory therapy consultation, or SICU admission), or pneumothorax within 365 days of the procedure, occur in 1.2 per 1000 of women after vaginal hysterectomy (Solomon et al. 2013). Venous thromboembolism after a vaginal hysterectomy occurs in 0.2% and is less common than with abdominal hysterectomy (Swenson et al. 2015).

6 Conclusion

Vaginal hysterectomy should be considered first line for all women having a hysterectomy and has been shown to be cost effective with low risk of complications.

7 Cross-References

- ▶ Abdominal Hysterectomy: Indications, Avoiding Complications
- ▶ Laparoscopic Hysterectomy
- ▶ Management of Abnormal Bleeding in Late Reproductive Years
- ▶ Management of Uterine Fibroids

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Pelvic Organ Prolapse: Diagnosis, Treatment, and Avoiding Complications

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Contents

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Abstract

Pelvic organ prolapse (POP) is defined as the descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina (vaginal vault or cuff scar after hysterectomy). Prolapse is extremely common and is one of the leading reasons for surgery in the United States.

The main symptom of prolapse is the sensation of bulge or pressure in the vagina. Severe prolapse may interfere with successful urination, defecation, or sexual function. Prolapse diagnosis is usually based on physical exam, though several formal staging systems exist. Asymptomatic or minimally symptomatic prolapse may not require any intervention. Patients with significant bother may elect to use a plastic device (pessary) to hold their prolapsed organs in place, or they may elect for surgery. There are a variety of surgical procedures for prolapse, depending on the patient's health, preferences, degree, and location of prolapse.

Keywords

Pelvic organ • Prolapse • Pessary • Surgery

1 Introduction

Pelvic organ prolapse (POP) is defined as the descent of one or more of the anterior vaginal wall, posterior vaginal wall, uterus (cervix), or apex of the vagina (vaginal vault or cuff after hysterectomy) (Haylen et al. 2010). POP is estimated to affect 3.3 million women in the United States alone, and the number of women affected is projected to increase by nearly 50% by 2050 (Wu et al. 2009). Prolapse is one of the most common reasons for surgery in the United States and is projected to increase from 166,000 surgeries annually in 2010 to 245,970 in 2050 (Wu et al. 2011).

The most common symptom of prolapse is the sensation or discomfort of vaginal or uterine tissue prolapsing from the vagina and between the legs (Fig. 1). Severe prolapse may be associated with sexual complaints and urinary symptoms such as voiding difficulty, bladder outlet obstruction, and detrusor overactivity (Romanzi et al. 1999). It is rare that prolapse will cause significant morbidity or mortality, but it is commonly associated with sexual, urinary, and defecatory symptoms that may interfere with activities of daily living and affect quality of life. It is not uncommon for women to digitally reduce their prolapse (splint) in order to urinate or defecate. In extreme cases, obstructed urination may result in obstructive uropathy causing hydronephrosis and even progressing to renal failure (Sudhakar et al. 2001).

Many patients with prolapse will elect for conservative management or go without treatment altogether (Culligan 2012). Conservative management strategies include pelvic floor muscle training and pessaries. A variety of surgical options are available, depending on the type and degree of prolapse, as well as patient preference and comorbidities. The necessity of hysterectomy at the time of prolapse repair is controversial, as is the need for mesh or graft to augment native tissue repairs.

2 Anatomy/Pathophysiology

Pelvic organ prolapse is the result of disruption of one or more of the supports that normally hold the pelvic organs in place. There are three primary supports of the uterus and upper vagina: 1) the cardinal/uterosacral ligament complex, 2) the lateral/paravaginal attachments of the endopelvic fascia, and 3) the perineal membrane (DeLancey 1992).

2.1 Level 1: The Cardinal and Uterosacral Ligament Complex

First, a note on terminology: Although the cardinal and uterosacral ligaments are commonly described as ligaments, true ligaments attach bone to bone, while the cardinal and uterosacral "ligaments" are more of a condensation of fibrous tissue, collagen, muscle, and nerves.

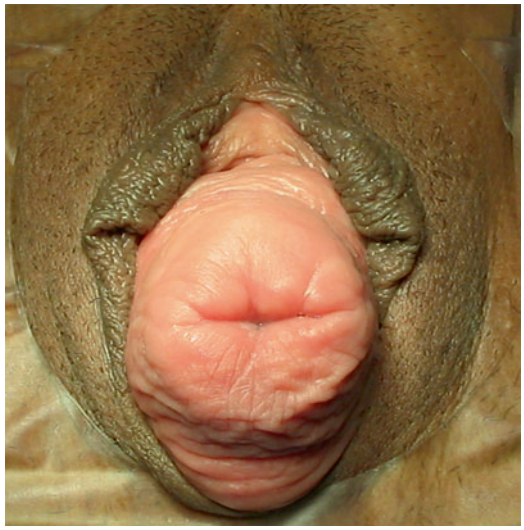

Fig. 1 Pelvic organ prolapse (Photograph courtesy of Dr. Begüm Özel)

The cardinal ligament stretches between the base of the uterus and the lateral wall of the pelvis, thereby preventing inferior movement of the uterus. The uterosacral ligament connects the lateral edge of the uterus to the anterior surface of the sacrum, which prevents the uterus from being displaced inferiorly and anteriorly (Drake et al. 2008).

These ligaments may be disrupted through surgical or obstetric trauma. However, it is more common that these ligaments are intact, but stretched out by consistent downward traction of the uterus and vagina. Similarly, collagen vascular disorders may be associated with lengthening and stretching of these ligaments and result in pelvic organ prolapse.

2.2 Level 2: The Endopelvic Fascia

Another note on terminology: The "endopelvic fascia" is not a true fascial layer, rather a condensation of areolar and connective tissue; however, it will hereafter be referred to as "fascia."

The endopelvic fascia is essentially the tendinous insertion of the levator ani complex where it attaches on the arch of the pelvis. This tendinous arch (arcus tendineus fascia pelvis) runs from the bottom of the pubic symphysis to the ischial spine on either side. Injury to this fascial layer or disruption of these lateral attachments is commonly seen after childbirth, even in the absence of a perineal laceration and is thought to be one of the primary causative factors for pelvic organ prolapse.

2.3 Level 3: The Perineal Body

The perineal body is the third and most distal level of support. This layer is made up of the superficial perineal muscles that form the anterior urogenital triangle (bulbocavernosus, ischiocavernosus, and transverse perineal). Within the triangle is a confluence of connective tissue that provides additional support to the vulva and lower vagina. Disruption of this layer may occur during childbirth, or due to chronic traction of the uterus and vagina due to defects in the upper two levels of support.

3 Risk Factors

The causes of prolapse are multifactorial. There are some genetic risk factors; a family history of prolapse is associated with increased risk, as is Caucasian race and Hispanic ethnicity, when compared to Asian and African Americans. The most common risk factors include vaginal childbirth, increasing age, and increasing body mass index. Vaginal childbirth is strongly associated with anatomic disruption of the pelvic organ supports, and pregnancy is associated with laxity/stretching of the pelvic floor ligaments. Increasing age is thought to be associated with changes in the collagen composition of the ligamentous supports, leading to increased risk of prolapse. Body mass index is likely a risk factor for prolapse due to chronic increases in abdominal pressure and straining. In fact, other causes of chronic increase in abdominal pressure have also been associated with prolapse (constipation, chronic cough) (Koelbl et al. 2013).

Although there have not been any proven effective strategies to reduce risk, it is reasonable

to think that weight loss, reduction of heavy lifting, treatment of constipation, modification of obstetric risk factors, and pelvic floor physical therapy may be effective in preventing the development or progression of pelvic organ prolapse.

4 Diagnosis

4.1 Patient History

As pelvic organ prolapse is rarely associated with significant morbidity or mortality, the most important principle in prolapse evaluation is assessing the degree of bother for the patient. The most effective strategy in managing prolapse is to allow the patient to express what aspect of the prolapse bothers her most. This allows the practitioner to tailor treatment plans to the patients' needs and wishes, rather than focusing on the anatomic outcomes that may or may not reflect successful treatment for the patient.

The most specific complaint of women with pelvic organ prolapse is the sensation of bulge or pressure in the vagina. This sensation may be difficult to distinguish from the sensation of pressure in the lower abdomen. Low abdominal pressure is often nonspecific, and, in the absence of vaginal pressure, is unlikely to be due to prolapse. Urinary, defecatory, and sexual symptoms are also common and should be evaluated in women with prolapse.

4.2 Physical Exam

Pelvic organ prolapse can almost always be evaluated completely with physical exam. Ancillary radiologic testing is rarely indicated. A comprehensive physical exam is indicated when considering any surgical intervention for pelvic organ prolapse. A complete evaluation should include: basic sensory testing, visual inspection of the external genitalia and cervix, bimanual and rectovaginal examination and visual assessment of prolapse with Valsalva. Additional testing for incontinence may be indicated in patients with urinary or fecal incontinence and some advocate testing for occult incontinence in women with prolapse considering surgical intervention.

4.3 Sensory Exam

Sensation to the vulva and perineum is primarily provided by the pudendal nerve, a branch of the S2–S4 nerve root. Intact sensation to the inner thigh and perineum to light touch and pinprick confirms function of the pudendal nerve to the cerebral cortex. The anal wink reflex or clitoral reflex requires an intact levator ani and pudendal nerves, as well as connection to the cerebral cortex. The anal wink may be checked by gently stroking perianally with the soft edge of a cotton swab; a positive test will result in contraction of the external anal sphincter. The clitoral reflex may be checked by gently squeezing the clitoris and looking for contraction of the pelvic floor. Both of these tests are specific but not sensitive, meaning that a positive test confirms intact nerves, but the absence of the reflex is not diagnostic of neurologic disruption.

4.4 Pelvic Exam

A careful speculum, bimanual, and rectovaginal exam is important to look for other etiologies of bulge in the vagina and to screen for cervical, vaginal, and vulvar cancers. The presence of prolapse does not increase the risk for any type of cancer, but prolapse may exist concomitantly with other gynecologic conditions, and these need to be ruled out.

Careful evaluation of the degree of prolapse must be documented for all patients with complaints of prolapse. The maximum amount of prolapse that can be elicited should be documented. This usually requires the patient to perform Valsalva or cough and may require the patient to

stand in order to demonstrate the maximum descent of her prolapse. Often, it is appropriate to separate a speculum and use the lower half to reduce the compartment not being evaluated. The posterior wall may be reduced in order to completely see and evaluate the anterior wall, and vice versa.

There are a variety of staging systems that have been proposed for prolapse. The most common are the Baden-Walker grading system and the Pelvic Organ Prolapse Quantification (POP-Q) staging system (Bump et al. 1996), which have been developed and endorsed by the International Continence Society and the International Urogynecological Association (Haylen et al. 2010).

The Baden-Walker grading system divides the vagina into three compartments: anterior, apical, and posterior. The anterior compartment consists of the upper vagina between the cervix and urethra and generally corresponds to the area just under the bladder and urethra. The apical compartment is the upper vagina and cervix, while the posterior compartment is the pelvic floor between the cervix and perineal body. Each compartment is considered separately and the maximum descent of each compartment evaluated. Prolapse in the upper half of the vagina is considered grade 1, in the lower half of the vagina is grade 2, coming out halfway is grade 3, and completely everted is considered grade 4 (Table 1). Such a grading system is easy to understand and remember and is often used by gynecologists to document the degree of prolapse (Baden and Walker 1992).

Table 1 Baden-Walker grading system for pelvic organ prolapse

Grade of Prolapse	Extent of prolapse in relationship to the hymen
Grade 0	Normal position for each respective site
Grade 1	Descent halfway to the hymen
Grade 2	Descent to the hymen
Grade 3	Descent halfway past the hymen
Grade 4	Maximum possible descent for each site

In an effort to further quantify prolapse and to describe and compare treatment outcomes, the POP-Q examination was developed. This technique is more complicated to learn, but is more quantitative and uses clear anatomic landmarks. It uses 9 points. All points of the POP-Q are measured in cm, relative to the hymen. Inside of the body are negative values, and outside of the body are measured as positive values. GH, PB, and TVL are measured at rest. The remainder of the points should be measured with the maximum prolapse elicited. Prolapse may be elicited with patient on Valsalva maneuver, with standing, or both (Table 2).

5 Complications of Prolapse

Significant complications from untreated pelvic organ prolapse are rare. The most common complications include vaginal abrasions, bleeding, and urinary retention. In rare cases, the prolapse may become so edematous that it is difficult or impossible to reduce – an incarcerated prolapse.

Vaginal abrasions or ulcerations with bleeding may be avoided with reduction of prolapse, either surgically or with pessary (Fig. 2). Vaginal abrasions related to atrophy may be treated with topical estrogen cream. Occasionally, the vaginal epithelium is so dry and irritated that additional treatment with Vaseline or vitamin A and D ointment is necessary.

Symptoms of urinary retention may be treated with reduction of prolapse. A recent study showed that in women with stage 3–4 prolapse, the prevalence of hydronephrosis was up to 55% (Dancz et al. 2015; Hui et al. 2011). Therefore, in women who decline intervention, it may be indicated to screen for retention with post-void residual, creatinine level, and renal ultrasound.

Prolapse that is traumatized, usually from a fall or other inadvertent harsh manipulation of the prolapse, may become edematous and irreducible. These may usually be reduced with adequate pain control and gentle, consistent pressure. The fundus must be gently aimed into the body in order to return the uterus to the pelvis.

Table 2 POP-Q staging system for pelvic organ prolapse

Aa – anterior wall 3 cm proximal to the urethral meatus (range, −3 to +3)	Ba – anterior wall Most distal part of the anterior wall	C – cervix or cuff Most distal descent of cervix/vaginal cuff
gh – genital hiatus Mid-urethral meatus to the posterior fourchette	pb – perineal body Posterior fourchette to the mid-anus	tvl – total vaginal length Greatest depth of the vagina when prolapse is reduced
Ap – posterior wall 3 cm proximal to the hymenal remnant (range, −3 to +3)	Bp – posterior wall Most distal part of the posterior wall	D – posterior fornix (omitted if there is no cervix)

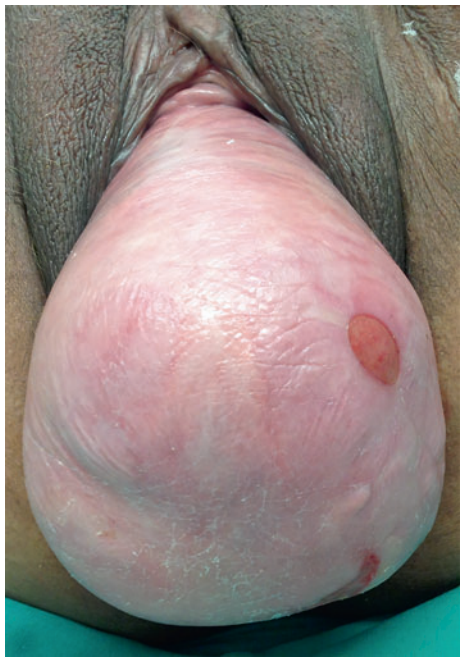

Fig. 2 Pelvic organ prolapse with ulcerations (Photograph courtesy of Dr. Begüm Özel)

6 Nonsurgical Management of Prolapse

6.1 Pessary

Pessaries are devices of various shapes and sizes that are placed in the vagina to reduce pelvic organ prolapse and restore normal anatomy. Pessary use can be temporary or long term. It provides immediate relief from pelvic organ prolapse symptoms, but requires some maintenance. Long-term pessary use may be an alternative to surgery in women with multiple comorbidities or in women who prefer to avoid surgical risks (Culligan 2012). Pessary use has been shown to be as effective as surgery in improving patients' symptoms of prolapse including bowel complaints, bladder complaints, sexual function, and overall quality of life (Abdool et al. 2011).

6.1.1 Fitting of Pessary

The success of pessaries lies in a proper fitting. Pessaries can be successfully fitted 60–90% of the time (Clemons et al. 2004; Lone et al. 2011). When a pessary is successful at the 4-week point, most women continue to use a pessary at 5 years (Lone et al. 2011). When choosing a pessary, the provider needs to consider the stage of pelvic organ prolapse, the size of vaginal vault, and the ability of the patient to manage their own pessary. The goal is to find the smallest pessary that effectively treats their prolapse symptoms. Initial fitting may require a trial of several different pessary types and/or sizes to adequately and comfortably reduce their prolapse (Culligan 2012).

Ring with support pessaries (Fig. 3) is widely available and the most commonly used (Cundiff et al. 2000). The initial choice of pessary size should be based on the examiner's bimanual exam and appreciation of the width of the vaginal canal (Culligan 2012). Once the exam is performed, the provider should identify an appropriate size and shape pessary. The pessary should be placed by the provider and tested by the patient. Initial tests for correct sizing can be performed by having the patient cough or stand with the pessary in place. If it stays in place, then the patient should attempt a Valsalva maneuver while sitting. If the

Fig. 3 Ring with support pessary

pessary continues to remain in place with these measures and is comfortable, it is likely the correct size. The patient should also be able to ambulate and urinate with the pessary in place. Well-fit pessaries should not be felt by the patient.

Once a pessary is successfully fit, the patient should return for close follow-up. Typically the patient is given a return appointment in 1–2 weeks to make sure the pessary continues to comfortably reduce the patient's prolapse and allows for normal daily functions (Trowbridge and Fenner 2007). At this time, if the patient is uncomfortable or has lost the pessary with activity, this is an opportunity to change pessary size or type. This visit also provides a good opportunity to educate a motivated patient on how to remove and clean her pessary so that she can manage her pessary at home. Once a patient is comfortable and has learned to manage her pessary, she can then be followed every 3–6 months. She is instructed to remove and clean the pessary with soap and water approximately once a week. If the patient is comfortable, but cannot change her own pessary, she should be seen every 2–3 months for outpatient exchange by her provider (Culligan 2012; Trowbridge and Fenner 2007).

6.1.2 Types of Pessaries

There are two general categories of pessaries – support and space filling. Support pessaries typically sit between the pubic symphysis and posterior fornix. They reduce prolapse by elevating the superior vagina and often have perforations that allow the escape of vaginal secretions. Examples of support pessaries are the ring, ring with support, Gehrung, and Hodge. Space-filling pessaries work by elevating the prolapse and maintaining the normal anatomic position by creating a barrier within the vagina that is larger than the genital hiatus. The cube pessary (Fig. 4) may be used for refractory cases, as it stays in place by creating suction to the vaginal walls. A commonly used option is the Gellhorn pessary, (Fig. 5) which acts both as suction and barrier (Cundiff et al. 2000). A randomized crossover trial showed no difference in patient satisfaction or symptom relief from the ring versus Gellhorn pessary (Cundiff et al. 2007).

The ring with support pessary is relatively easy to place/remove and is well tolerated by patients (Cundiff et al. 2000). If the ring with support does not work, the next choice is typically the Gellhorn. If neither of these work, chances of successful prolapse management with pessary are unlikely (Culligan 2012). A variety of other pessaries may be used, each with slightly different features. Overall, these pessaries are typically more difficult for patients to manage (Culligan 2012; Trowbridge and Fenner 2007). The inflatoball (Fig. 6) is an option for women with stage 3 or 4 pelvic organ prolapse who desire the ability to manage their pessary at home. It is more easily placed and removed by the patient compared to a Gellhorn or donut pessary because it can be inflated after insertion and deflated prior to removal, though the stem does protrude from the vagina and may cause discomfort for the patient (Trowbridge and Fenner 2007).

Pessaries are generally made of surgical-grade silicone; therefore, patients with latex allergies may use them without concern. Over time, the silicone may develop some discoloration. The structural integrity of the pessary is not affected, and discolored pessaries may be used indefinitely. The inflatoball pessary (Fig. 6) is the only pessary that is made of rubber. The rubber material in the inflatoball pessary may absorb a slight odor, and the rubber may dry out over time. Inflatoball pessaries should be checked and replaced periodically.

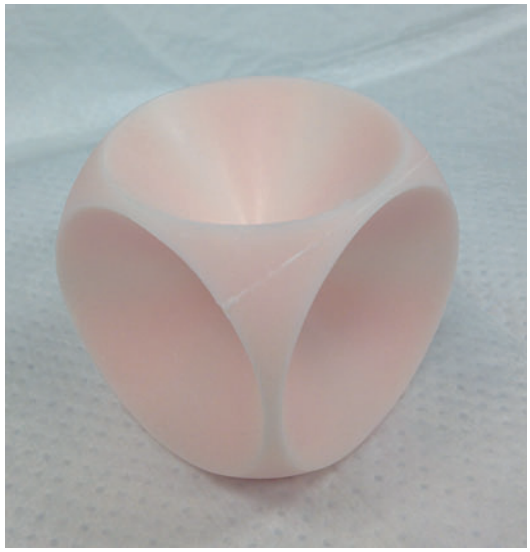

Fig. 4 Cube pessary

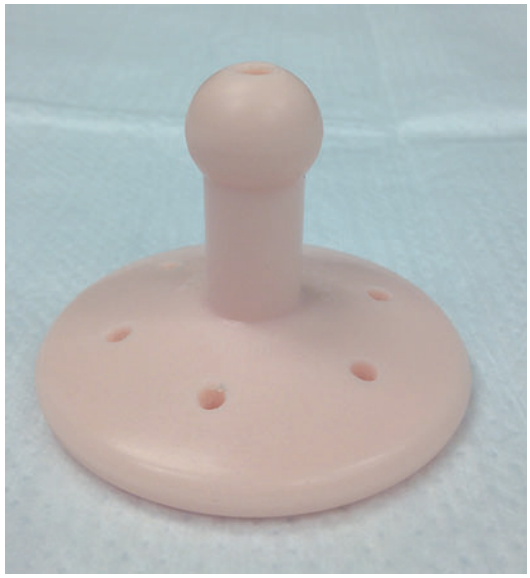

Fig. 5 Gellhorn pessary

6.1.3 Complications

Reported complication rates from pessaries vary, but in a large study of over a thousand women, 88.5% had no complications (Hanson et al. 2006). The most commonly reported complications are vaginal discharge, vaginal ulcerations, and abrasions. It is normal for women to have increased vaginal discharge with a pessary in place, but there is concern for infection if they report itching, foul odor, or burning sensation. With a pessary in place, the vaginal flora is altered, and women are more predisposed to bacterial vaginosis (Alnaif and Drutz 2000). A vaginal wet prep will distinguish between bacterial vaginosis and physiologic discharge and should be used prior to administration of antibiotics. If the patient is bothered by the physiologic vaginal discharge, it may be alleviated by more frequent removal and cleaning of the pessary.

Vaginal ulcerations or abrasions due to local pressure effects are also common and typically occur if the pessary is left in place over time. Symptoms of vaginal ulcerations or abrasions include discharge, odor, and bleeding. If the patient can change it herself, the pessary may be removed for a few hours or overnight and replaced. At each follow-up visit, a speculum exam should be performed to evaluate for the presence of any ulcerations or abrasions. The patient should also be instructed to make an appointment if she notices any vaginal bleeding. Vaginal abrasions and ulcerations may be treated with removal of the pessary for a few weeks, and use vaginal estrogen cream on a daily basis for a short-term course (Clemons et al. 2004; Trowbridge and Fenner 2007). The patient should be followed regularly until the ulceration has resolved, and then the pessary may be replaced with continued use of vaginal estrogen cream two to three times a week (Trowbridge and Fenner 2007).

Another potential side effect of pessary is urinary incontinence. Typically, it is the reduction of prolapse and return of normal anatomic positioning of the urethra that may unmask occult incontinence or worsen existing incontinence. In cases with incontinence, a specific incontinence pessary (incontinence ring, incontinence dish, or incontinence dish with support) may be used. The incontinence pessaries have an additional knob to provide support at the urethrovesical junction (Trowbridge and Fenner 2007).

Severe complications with pessary are rare. Pessary impaction can occur if a pessary is in place for a prolonged period of time without removal. There have been case reports of severe complications from

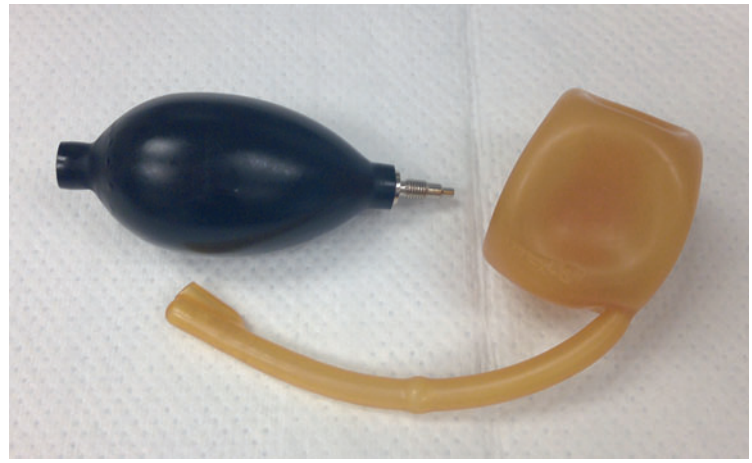

Fig. 6 Inflatoball pessary

pessaries, including impaction of or erosion into the urethra, rectum, or cervix (Figs. 7 and 8). Potential for compression of the urethra should be evaluated at pessary placement; anyone who cannot urinate should have the pessary removed and a smaller one placed. Obstructed voiding may lead to urinary retention, infection, and urosepsis (Wheeler et al. 2004). Rectal compression can lead to obstructed defecation or bowel obstruction (Roberge et al. 2001). Some pessaries are designed with a central space, through which the cervix may prolapse and become incarcerated (Thubert and Deffieux 2014). There are case reports of pessaries left in situ for years that then erode into the bladder or rectum (Arias et al. 2008; Rogo-Gupta et al. 2012).

These severe complications may be avoided with regular pessary removal and replacement. It is also reasonable to advise patients to confide in a family member or close friend of the presence of the pessary. In case of accident or incapacitation, someone should be aware the pessary should be removed at least once every 3 months.

7 Pelvic Floor Muscle Training

Pelvic floor muscle training has been suggested as management for mild to moderate prolapse. It consists of both sessions with a trained therapist to assess muscle strength and teach exercises for muscle strengthening and regimented exercise programs for the patient to complete at home. The goal of pelvic floor muscle training is to increase muscle volume and thereby diminish the size of the levator hiatus and provide improved structural support for the pelvic organs (Bø 2006). A prospective randomized trial demonstrated that with regimented pelvic floor muscle training over the course of 6 months, women with up to stage 3 pelvic organ prolapse were able to symptomatically and objectively improve their pelvic organ prolapse (Braekken et al. 2010). That study also demonstrated increased muscle thickness, elevated location of the bladder and rectum, and decreased hiatal size with the regimented exercises. Similar improvement in symptoms and reduction of prolapse have been reported in women with training as brief as 14 weeks with improved symptoms and up to stage 2 improvement of pelvic organ prolapse as measured by the POP-Q, though the majority showed no change or reduction of stage 1 of pelvic organ prolapse (Hagen et al. 2009; Stüpp et al. 2011). Limitations of this course of therapy are patient motivation and access to trained therapists.

8 Surgical Management

A variety of surgical treatments are available for pelvic organ prolapse. The choice of surgery depends on many factors including compartment of prolapse, severity of prolapse, patient health and overall treatment goals, prior surgeries, and

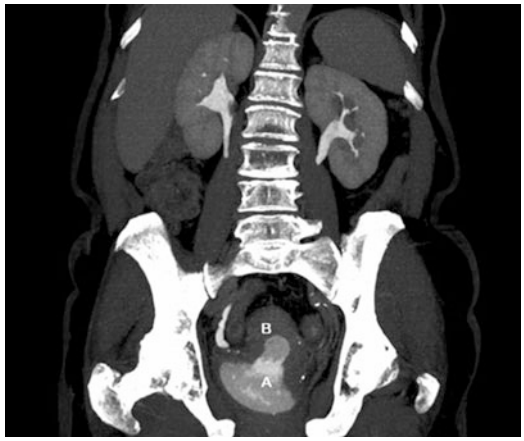

Fig. 7 Computed tomography (*CT*) of intravesical pessary demonstrating a Gellhorn pessary (*A*) located in the bladder (*B*) (Originally published in Rogo-Gupta L, Le NB, Raz S. Foreign body in the bladder 11 years after intravaginal pessary. Int Urogynecol J 2012; 23:1311–1313; with kind permission of © Springer Science+Business Media. All Rights Reserved)

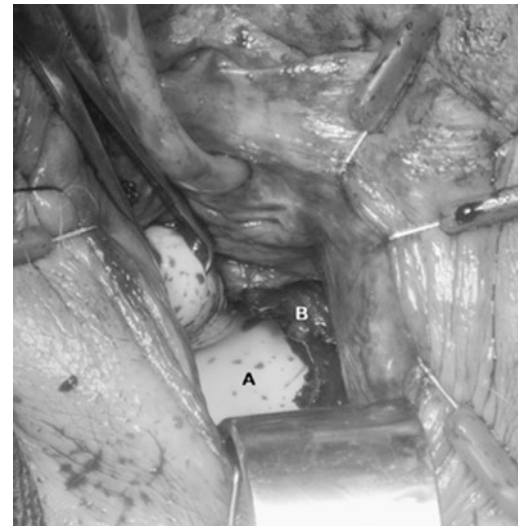

Fig. 8 Intraoperative image of pessary (*A*) within the bladder (*B*) (Originally published in Rogo-Gupta L, Le NB, Raz S. Foreign body in the bladder 11 years after intravaginal pessary. Int Urogynecol J 2012; 23:1311–1313; with kind permission of © Springer Science+Business Media. All Rights Reserved)

surgeon preference. Graft or mesh augmentation may be considered in select cases. The surgical techniques used for pelvic organ prolapse can broadly be categorized by compartment: anterior, apical, and posterior.

9 Anterior Prolapse

The anterior compartment is the most common site of pelvic organ prolapse and the most difficult to repair. Anatomic and symptomatic outcomes after surgical repair are generally good, but when prolapse recurs, it is most commonly in the anterior compartment.

10 Anterior Colporrhaphy

The mainstay of surgical management of anterior prolapse is the anterior colporrhaphy (Fig. 9). During this procedure, a transverse incision is made at the apex of the anterior vagina (if concurrent hysterectomy is performed, then the anterior colpotomy site may be used). The anterior vagina is then put on traction using Allis clamps, to essentially evert the anterior wall (or ceiling of the vagina). Using Metzenbaum scissors, the anterior vaginal epithelium is undermined to separate it from the underlying muscularis. This epithelium is then incised in a linear fashion from the apex of the vagina to approximately 3–4 cm below the urethral meatus. Allis clamps or Pratt-Smith clamps may be placed on the cut edge of the epithelium, and the epithelium dissected off the underlying muscularis. This dissection is extended laterally to the pelvic sidewall. The underlying muscularis is then plicated with a series of U stitches of 0 polyglactin suture. These stitches should be placed along the junction of where the epithelium has been dissected off the muscularis, taking care that the tissue plicated is the muscularis and not the vaginal epithelium. While these sutures are tied down, the underlying prolapsed tissue is reduced. The result is a midline reduction of the anterior prolapse. The excess vaginal epithelium is then trimmed, and the epithelium is plicated in the midline using 2–0 polyglactin suture.

Studies on the success of prolapse repair are difficult to compare, as different outcomes are often reported. Symptomatic success does not necessarily require anatomic success, and often

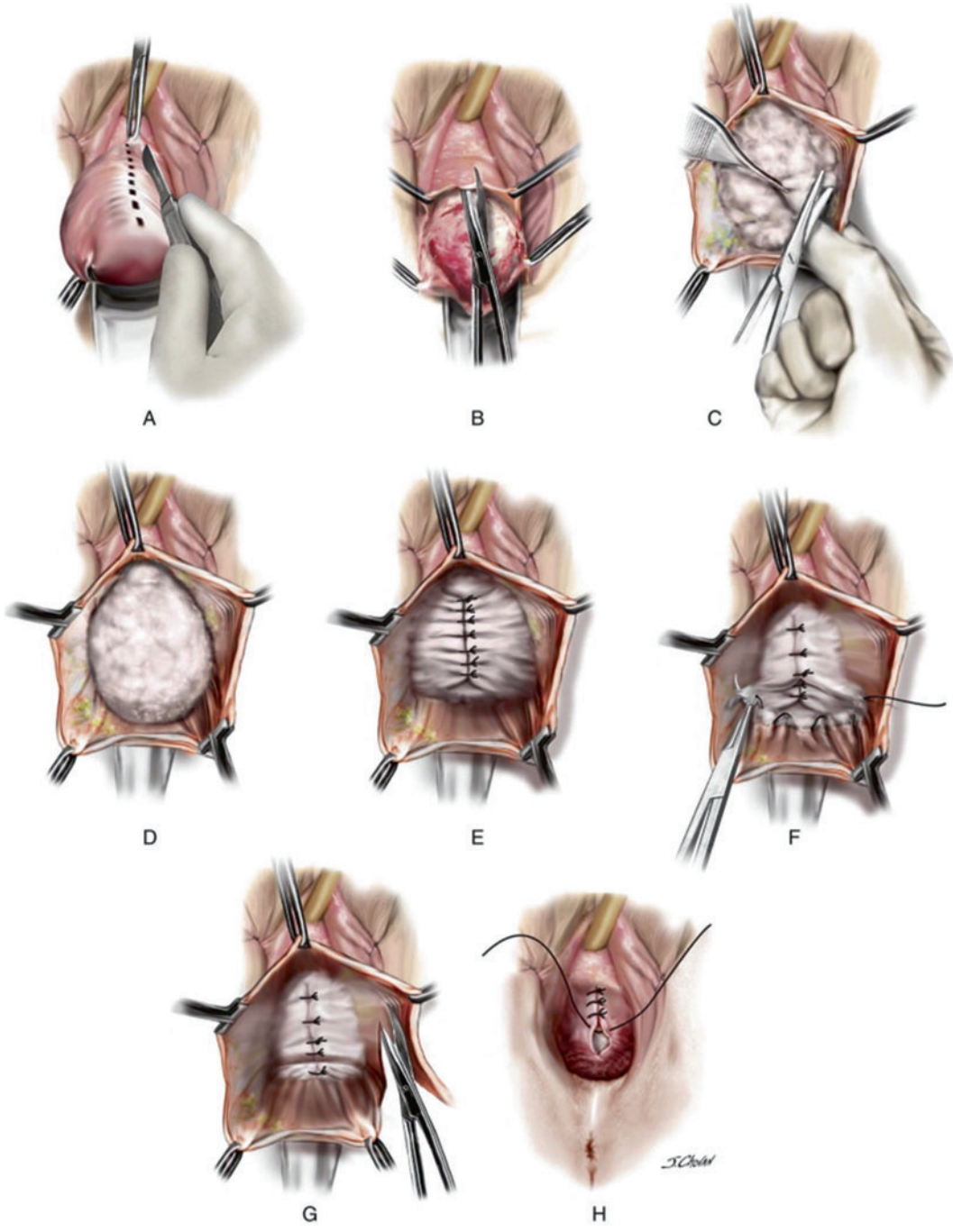

Fig. 9 Traditional anterior colporrhaphy. (**a**) Initial midline anterior vaginal wall incision. (**b**) Midline incision is extended. (**c**) Sharp dissection of the bladder off the vaginal wall. (**d**) The bladder has been mobilized off the vagina. (**e**) Initial plication layer is placed. (**f**) Second plication layer is placed. (**g**) Trimming of excess vaginal epithelium. (**h**) Closure of vaginal epithelium (Reprinted from Surgical Management of Pelvic Organ Prolapse, 1st Edition, Maher CF, Karram M. Surgical Management of Anterior Vaginal Wall Prolapse, p117–137, with kind permission from Elsevier)

both are reported as separate measures. In general, the reported success rates of anterior colporrhaphy range from 80% to 100% in retrospective series, though in prospective studies, the rates are much lower (30–55%) (Menefee et al. 2011; Nguyen and Burchette 2008; Weber et al. 2001).

Multiple procedures have been developed to try to improve anatomic and symptomatic outcomes of anterior colporrhaphy. Variations on the anterior colporrhaphy include the paravaginal (or ultralateral) repair, site-specific repair, anterior colporrhaphy with mesh augmentation, and anterior colporrhaphy with graft augmentation. Several studies have compared reoperation rates, as well as anatomic and symptomatic outcomes between these procedures. In general, anatomic outcomes are slightly better using mesh or graft augmentation, but the symptomatic outcomes and reoperation rates are the same between procedures (Maher et al. 2013).

10.1 Vaginal Paravaginal Repair

Some surgeons advocate an ultralateral approach to anterior colporrhaphy, referred to as a vaginal paravaginal repair (Fig. 10). The paravaginal repair is based on the theory that prolapse may be caused by a detachment of the underlying muscularis from its lateral attachments to the arcus tendineus fascia pelvis (ATFP). This technique involves opening the anterior vaginal wall, similar to the dissection used in a traditional anterior colporrhaphy as described above. The vaginal epithelium is dissected off the underlying muscularis farther laterally than for a traditional anterior colporrhaphy, and the paravaginal space is developed between the obturator internus muscle and the vaginal muscularis layer. This space is extended along the ischiopubic rami using palpation in order to identify the ischial spines and the ATFP. The ATFP runs between the pubic symphysis and the ischial spine on either side. The ATFP is palpated and then visualized using Breisky-Navratil retractors. Upon clear identification of the ATFP, three to six sutures of 0 polyglactin suture are placed through the ATFP. These sutures may be held if a concomitant anterior colporrhaphy or apical suspension is being performed. The sutures through the ATFP are then brought through the muscularis tissue close to the midline, so that the muscularis is brought up and laterally toward the ATFP. The stitch is then carried to the underside of the vaginal epithelium. This technique obliterates the paravaginal space and essentially brings the epithelium, the muscularis, and the ATFP into close approximation. The excess vaginal epithelium is trimmed, and the vaginal epithelium is reapproximated in the midline.

This technique has a high success rate (67–100%), which is tempered by complications including bilateral ureteric obstruction, retropubic hematomas, abscesses, and transfusion (Maher et al. 2013). This procedure may be performed abdominally or laparoscopically, but requires a high degree of surgical skill, and efficacy data is limited.

10.2 Site-Specific Repair

An additional variation of the anterior colporrhaphy is a site-specific repair. The concept behind this repair is that although some cases of anterior prolapse are due to complete separation of the muscularis from its lateral attachments, other cases of anterior prolapse are due to specific defects in the muscularis. When these defects are sought out and identified during anterior colporrhaphy, they should be repaired individually. A midline plication may be performed at the same time as a site-specific repair.

10.3 Graft and Mesh Augmentation

Due to the relatively high failure rates of prolapse repairs, there has been significant interest in augmenting repairs with synthetic or biologic materials. Although mesh and graft augmentation has been used with wide success in the hernia repair literature, vaginal augmentation has been more controversial. Generally, mesh or graft augmentation may be considered for patients who fail a native tissue repair.

The technique for the placement of synthetic mesh or biologic graft is essentially the same. Several companies have developed prefabricated meshes to fit the various vaginal compartments.

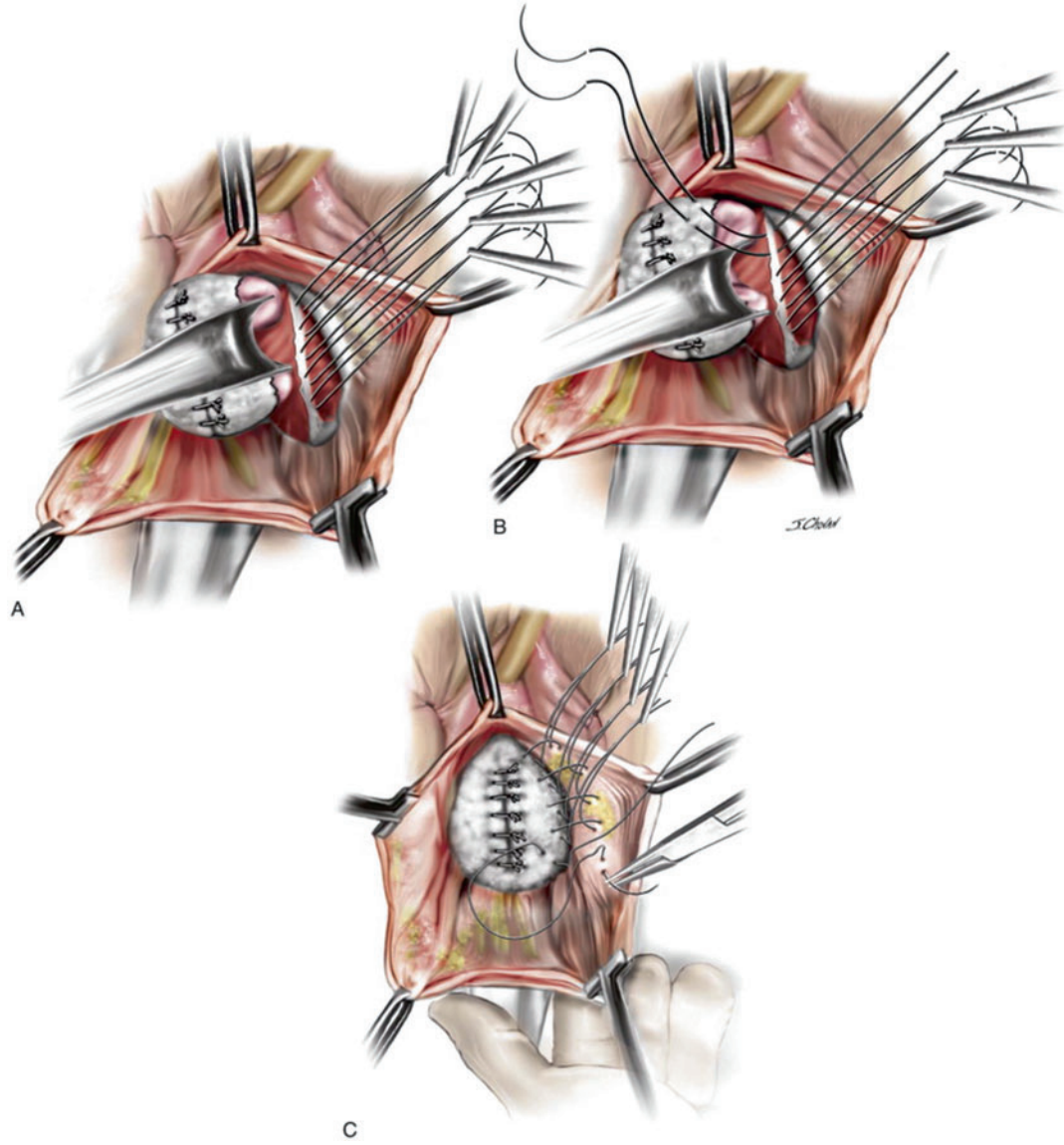

Fig. 10 Vaginal paravaginal repair. (**a**) Numerous sutures are passed through the arcus tendineus fascia pelvis (*white line*). (**b**) Each suture is passed through the edge of the detached fascia. (**c**) Each suture is passed through the vaginal wall excluding the epithelium (Reprinted from Surgical Management of Pelvic Organ Prolapse, 1st Edition, Maher CF, Karram M. Surgical Management of Anterior Vaginal Wall Prolapse, p117–137, with kind permission from Elsevier)

These mesh kits vary in size and shape of the mesh, as well as the introducer to fix the mesh to the vaginal tissues. Many of the kits use a trocar introducer to fix the apical portion of the mesh to the sacrospinous ligament, and the lateral or distal portion of the mesh may be sutured to the ATFP (as described above for a paravaginal repair) or may be trocar guided through the obturator space.

When a kit is not used, the mesh or graft may be cut to fit the patient's anterior vaginal wall. The vaginal wall is incised in the midline, taking care to dissect full thickness through the vaginal muscularis down to the bladder. This is in contrast

to the anterior colporrhaphy, where the vaginal epithelium is split from the underlying muscularis. After dissection of the epithelium and muscularis off the bladder, the graft/mesh is placed loosely under the tissue and sutured to the ATFP laterally. The overlying vagina is not trimmed and is then reapproximated in the midline.

10.4 Types of Grafts

10.4.1 Biologic Grafts

Biologic grafts may be used as an alternative to synthetic mesh grafts. Biologic graft options include:

Autograft – graft material is harvested from the patient herself. Generally it is taken from the rectus sheath or fascia lata. The use of autologous fascia has the advantage of lower risk of infection and host rejection. The size of the graft is generally 6–8 cm long and 4 cm wide. The harvest of an autologous fascial graft of this size may be associated with significant morbidity and is rarely used. It may be considered in patients with contraindications to mesh (Cormio et al. 2015).

Allograft – fascial material is harvested from donor or cadaveric tissue. Several small studies have demonstrated success rates ranging from 81% to 100%, with acceptable complication rates, though the only randomized controlled trial failed to show an improvement over traditional anterior colporrhaphy. Concerns regarding prior transmission and residual antigenicity resulting in host-graft reactions have limited the acceptance of allograft materials for prolapse repair.

Xenograft – Porcine dermis, porcine small intestine submucosa, bovine pericardium, or bovine dermis. Xenografts have been used in the anterior compartment with mixed results. One study retrospectively compared anterior colporrhaphy, porcine dermis, and polypropylene graft, with the porcine dermis significantly less effective than the other two treatments, with a 21% rate of vaginal extrusion of the porcine dermis. Other groups have found much better success rates, with graft extrusion rates of 1–17% (Maher et al. 2013). A Cochrane meta-analysis found that when graft was used to augment the anterior compartment, the objective failure rate was higher than when no graft was used (Maher et al. 2013).

Overall, some advocate biologic grafts as an alternative to synthetic mesh, although no subjective benefit has been reported by patients, and the complication rates are similar to synthetic meshes. Biologic grafts should be considered in patients who refuse synthetic meshes or those with contraindications to synthetic mesh. Synthetic mesh is contraindicated in patients who have had a prior mesh complication and those who desire future fertility (as the synthetic meshes do not stretch). Biologic grafts may be preferred to synthetic meshes in patients with impaired wound healing such as those with prior pelvic irradiation. Both meshes and grafts should be used with caution in patients with chronic pelvic pain, endometriosis, painful bladder syndrome, vulvodynia, and other vulvar pain disorders.

11 Transvaginal Mesh for Anterior/Apical Prolapse

Starting in 2004, a variety of prepackaged kits were introduced to augment prolapse repair in the vagina (Figs. 11 and 12). These kits use a variety of techniques to augment the anterior, apical, and posterior compartments. There is reasonable evidence to support that anatomic outcomes in the anterior and apical compartments are improved relative to native tissue repairs (Maher et al. 2013). However, there is no difference in patient subjective improvement, quality of life measures, or reoperation rates for prolapse. The improvement in anatomic outcomes comes at the cost of increased complications related to the mesh, with mesh erosion rates reported up to 25% (Maher et al. 2013). The consequences of mesh

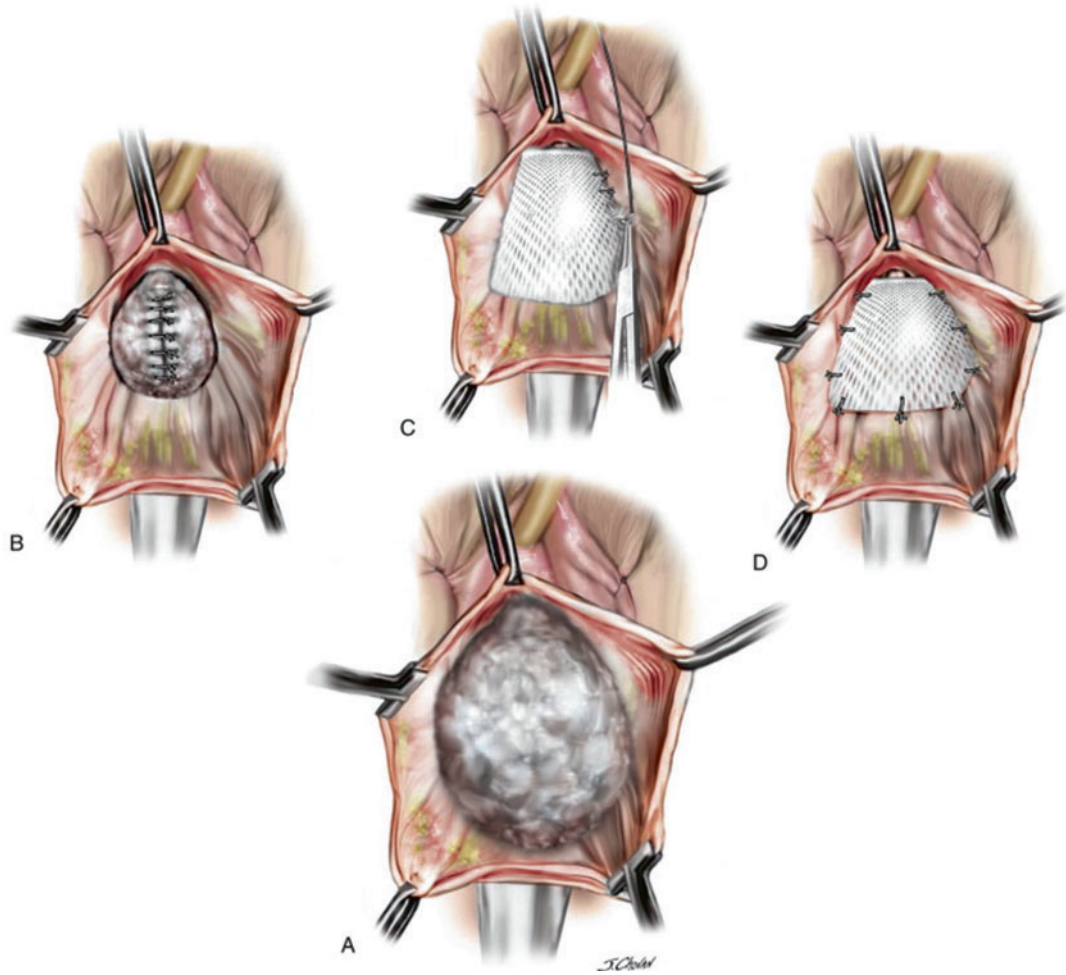

Fig. 11 Mesh augmentation of anterior wall prolapse repair. (**a**) Anterior prolapse is visualized. (**b**) Midline plication is completed. (**c**–**d**) Self-styled mesh is sutured in place (Reprinted from Surgical Management of Pelvic Organ Prolapse, 1st Edition, Maher CF, Karram M. Surgical Management of Anterior Vaginal Wall Prolapse, p117–137, with kind permission from Elsevier)

complications can be significant and often result in reoperation. These findings prompted the FDA to release an alert about transvaginal mesh placement in 2011. The alert essentially states that mesh may improve outcomes, but the complications in most cases outweigh the benefits. However, it is important to note that no transvaginal mesh has been recalled and that in selected patients who are appropriately counseled, transvaginal mesh augmentation may be preferred to more invasive, abdominal procedures.

11.1 Concomitant Hysterectomy

The role of concomitant hysterectomy for anterior prolapse is controversial. The uterus, if normal and not significantly prolapsed, may be left in situ during anterior colporrhaphy. However, anterior prolapse rarely occurs in isolation and is most commonly associated with apical (uterine) prolapse. Support of the apex is important to creating a durable and effective repair of the anterior wall (Hsu et al. 2008; Rooney et al. 2006). Many of the

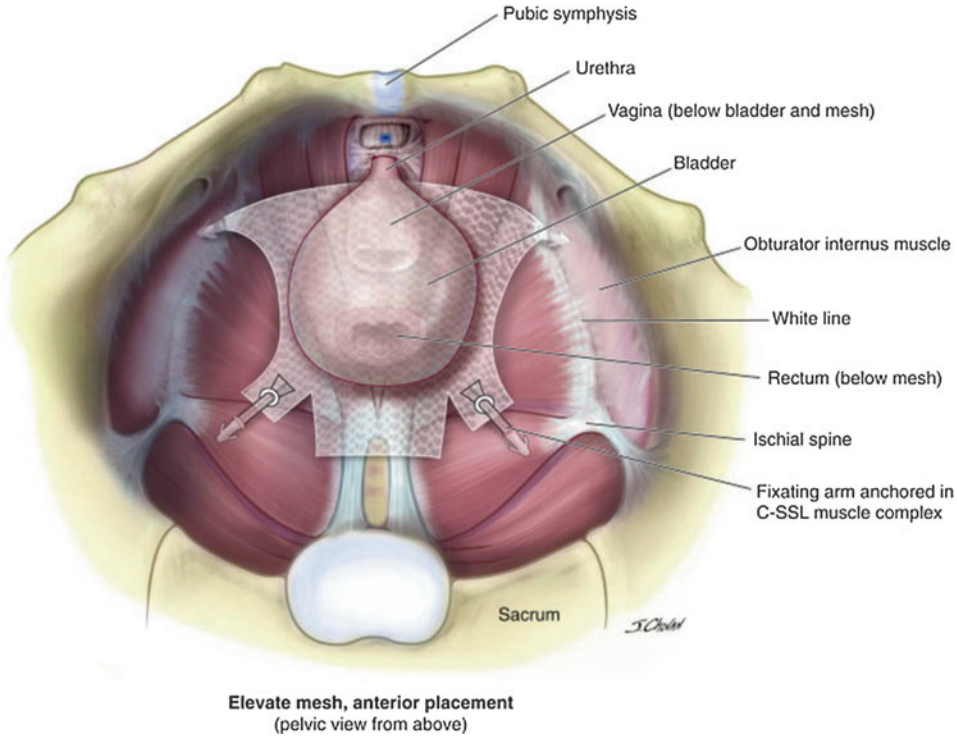

Fig. 12 Transvaginal mesh kit for anterior/apical prolapse. The elevate incisionless mesh (American Medical Systems) is bilaterally anchored to the sacrospinous ligament and obturator internus muscle near the distal end of the arcus tendineus fascia pelvis (Reprinted from Surgical Management of Pelvic Organ Prolapse, 1st Edition, Maher CF, Karram M. Surgical Management of Anterior Vaginal Wall Prolapse, p117–137 (2013); with kind permission from Elsevier)

apical suspension techniques described below can be adapted to leave the uterus in situ. The decision to remove the uterus must be approached by the physician in consultation with the patient and take into account the patient's comorbidities, degree of prolapse, and preferences, as well as the surgeon's experience with the surgical procedures.

12 Apical Prolapse

Apical prolapse includes descent of the uterus and the vault after prior hysterectomy. Apical prolapse repairs generally have good results, and there are a variety of approaches to apical prolapse. Apical repairs can broadly be categorized into vaginal, abdominal, and obliterative approaches. Abdominal repairs may be performed via laparotomy, laparoscopy, or robotically.

13 Vaginal Approach for Apical Prolapse

13.1 Mayo/McCall Culdoplasty

One of the most common procedures for apical suspension, the Mayo/McCall culdoplasty, is often performed at the time of vaginal hysterectomy for non-prolapse indications. There are a number of variations, but there are several key steps to the Mayo/McCall culdoplasty (Fig. 13). After removal of the uterus, the vaginal cuff is examined for hemostasis. The vaginal cuff is transfixed to the cut edges of the uterosacral ligaments in order to suspend the cuff within the vagina. One to three sutures are placed through the uterosacral ligament as high as possible. Sequential bites are taken superficially across the peritoneum overlying the rectum until the opposite uterosacral

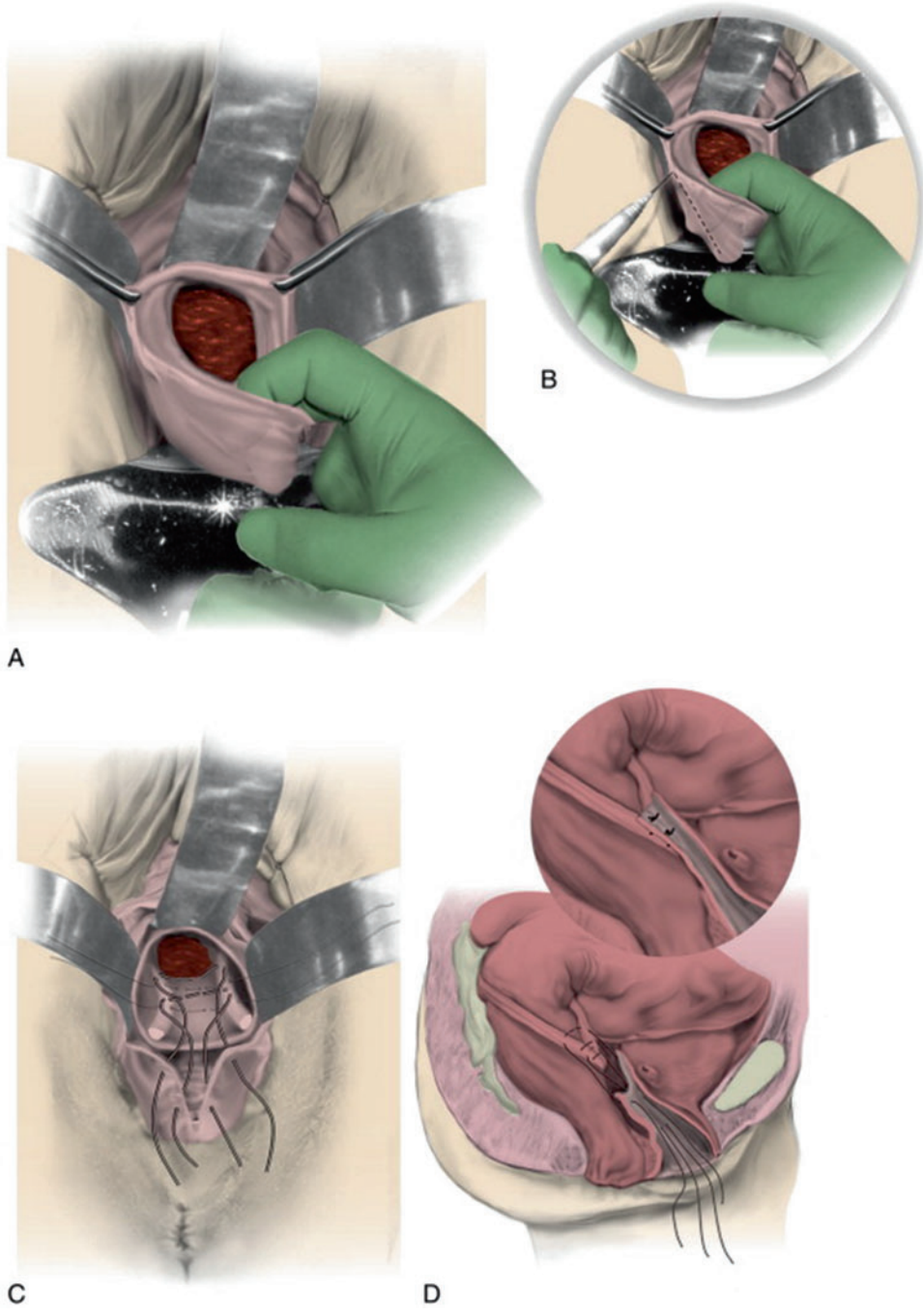

Fig. 13 Modified McCall culdoplasty. (**a**) The cul-de-sac is palpated and excessive peritoneum and posterior vaginal wall are noted. (**b**) A wedge of tissue (*dotted line*) is excised to decrease the caliber of the upper portion of the posterior vaginal wall. (**c**) External McCall stitches are placed in the traditional fashion. (**d**) Tying these sutures obliterates the cul-de-sac, supports the vaginal cuff, and increases posterior vaginal wall length (Reprinted from Urogynecology and reconstructive pelvic surgery, 4th Edition, Karram MM, Ridgeway BM, Walters MD. Surgical treatment of vaginal apex prolapse, p360–382. (2015); with kind permission from Elsevier)

ligament is sutured. When tied down, the uterosacral ligaments are plicated in the midline, and the posterior cul-de-sac is obliterated. Variations on this procedure are commonly performed, but outcome data is limited. The few retrospective studies available show success rates of up to 85%, with reoperation rates ranging from 0% to 14% (Barber and Maher 2013).

14 Uterosacral Ligament Suspension

14.1 Technique

Much of the support of the uterus comes from the cardinal/uterosacral ligament complex (Level 1 support). Uterosacral ligament suspension uses the patient's own ligaments to suspend the vaginal cuff above the level where the uterus has been amputated (Fig. 14). After the uterus is removed, the cuff is examined for hemostasis (if hysterectomy is not performed, the vaginal apex is grasped and incised). The ischial spines are identified and palpated intraperitoneally. The cut edge of the uterosacral ligament is grasped with Allis clamps on either side (at approximately 5:00 and 7:00 on the clockface). Traction allows for palpation of the uterosacral ligaments. Several sutures of permanent or delayed absorbable suture are placed through the uterosacral ligament at the level of the ischial spine. This procedure is repeated on the opposite side. The distal edge of the uterosacral ligaments is then plicated in the midline to obliterate the cul-de-sac. The highest delayed absorbable suture is placed full thickness through the posterior vaginal wall. If necessary, an anterior colporrhaphy may be performed. The vagina is trimmed and closed with 0 or 2-0 absorbable suture. After closure of the vagina, the uterosacral sutures are tied down on either side with suspension of the vault. Abdominal and laparoscopic approaches to this procedure have also been described.

14.2 Outcomes and Complications

Outcomes after uterosacral ligament suspension are generally good, with anatomic success ranging from 81% to 98%, and symptomatic improvement in 82–100% of patients (Margulies et al. 2010). In a recent large, prospective, randomized, controlled trial, the composite outcome of anatomic success and subjective success and lack of reoperation were reported to be 59.2% (Barber et al. 2014). The most commonly identified complication is ureteral injury or kinking, which should be looked for and identified intraoperatively. Ureteral kinking can be managed by removal of the offending suture and usually requires no further intervention. The incidence of ureteral injury or kinking ranges from 1% to 11% (Margulies et al. 2010) with most studies reporting a low incidence. However, intraoperative cystoscopy is highly recommended to ensure ureteral patency.

15 Sacrospinous Ligament Fixation

15.1 Technique

The sacrospinous ligaments extend from the ischial spines to the lower portion of the sacrum and coccyx and should be palpated prior to initiation of the procedure. The vagina is typically fixed unilaterally to the sacrospinous ligament, though bilateral fixations have been described. The posterior vaginal wall is incised in the midline and the vaginal epithelium dissected off the rectovaginal fascia. If an enterocele is encountered, it should be dissected off the posterior vaginal wall and closed with a high purse-string suture. The dissection of the epithelium off the rectovaginal fascia is extended laterally to identify the arcus tendineus fascia pelvis. The perirectal space is identified in this area by using blunt or sharp dissection and by mobilizing the rectum medially. The ischial spine is identified, and the

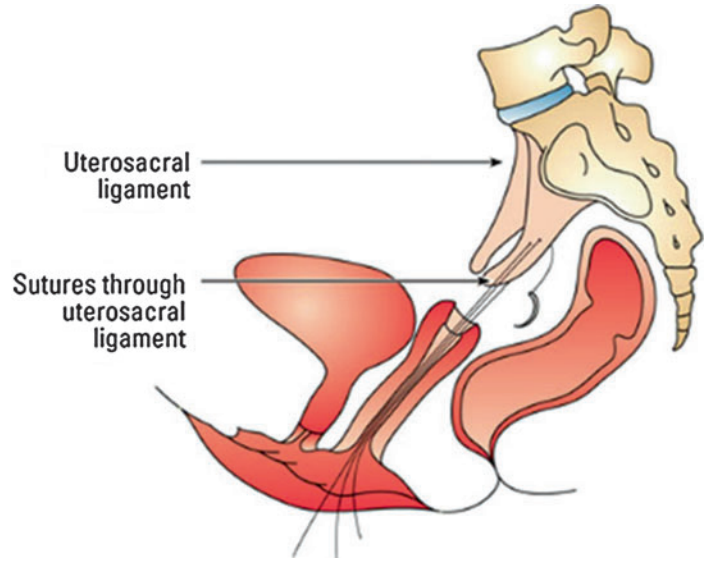

Fig. 14 Uterosacral ligament suspension. The vaginal cuff is fixed to the cut uterosacral ligaments on either side at the level of the ischial spines (Originally published in Cvach K, Dwyer P. Surgical management of pelvic organ prolapse: abdominal and vaginal approaches. World J Urol 2011;30 (4):471–7; with kind permission of Springer Science+Business Media. All Rights Reserved)

sacrospinous ligament is palpated dorsal and medial to the ischial spine. Once the ligament is identified, a rectal exam should be performed to confirm that no inadvertent injury has occurred. A suture is then passed through the sacrospinous ligament. The position of the ligament makes this suture passage difficult, and a variety of instruments have been designed to facilitate passage of the suture through the sacrospinous ligament. Commonly used techniques include the long-handled Deschamps ligature carrier, the Miya Hook, or proprietary instruments such as the Capio Suture device (Boston Scientific) (Figs. 15 and 16) or the Nichols-Veronikis ligature carrier (Cooper).

15.2 Outcomes and Complications

Overall, outcomes for sacrospinous ligament fixation are similar to uterosacral ligament suspension. A large randomized trial compared the two and found no significant difference in composite outcome of 60.5% at 2 years (composite outcome combines: anatomic success and subjective success and no reoperation) (Barber et al. 2014). The most commonly reported complication of sacrospinous ligament fixation is buttock pain, which is seen in 12.4% of cases (Barber et al. 2014). Such pain is usually self-limiting and should resolve completely by 6 weeks postoperatively. Additional rare but serious intraoperative complications have been reported, including hemorrhage (0.2%) and rectal injury (0.4%) (Sze and Karram 1997). Hemorrhage may result from laceration of the inferior gluteal vessels, the hypogastric venous plexus, or the internal pudendal vessels. If a rectal injury occurs, it can usually be repaired transvaginally.

16 Alternative Vaginal Approaches

Several procedures have been described for the suspension of the vaginal vault, with or without hysterectomy. The most notable of which are the levator myorrhaphy and the iliococcygeus fascial suspension.

The technique for the levator myorrhaphy involves a wide plication of the levator muscles and fixation of the vaginal cuff to the plicated

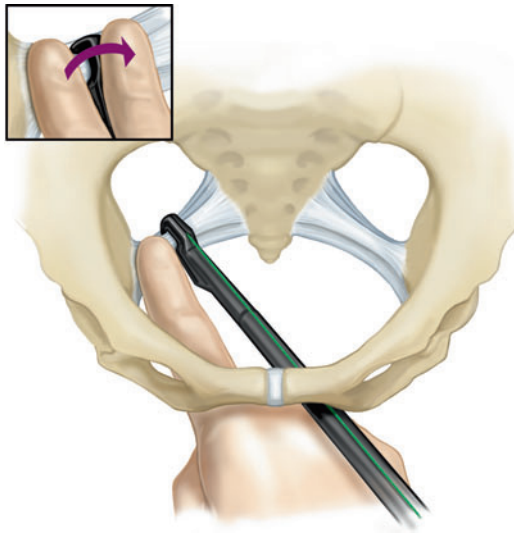

Fig. 15 Suture device for sacrospinous ligament fixation. The sacrospinous ligament is palpated at the level of the ischial spine. The suture device is placed medial to the operator finger, and the suture is passed through the ligament (Image reproduced with kind permission from Boston Scientific)

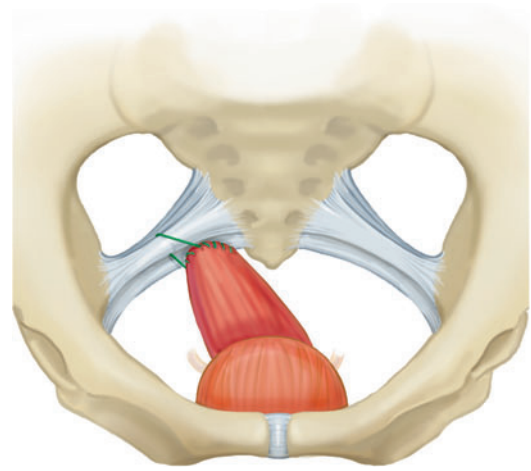

Fig. 16 Sacrospinous ligament fixation. The apex of the vagina is fixed unilaterally to the sacrospinous ligament (Image reproduced with kind permission from Boston Scientific)

muscles (Francis and Jeffcoate 1961). Packing is placed in the rectum to avoid narrowing of the rectum. Comparative studies to uterosacral ligament suspension have shown no difference in anatomic success or subjective outcomes; however, the total vaginal length was shorter after levator myorrhaphy (7.9 vs. 8.9 cm, $p = 0.04$) (Natale et al. 2010).

Iliococcygeus fascial suspension is also known as the Inmon technique (Inmon 1963). It is used to suspend the vaginal apex to the iliococcygeus fascia just below the ischial spine. The initial studies describing the procedure reported a case series of 152 patients. In that initial series, four intraoperative complications occurred (one rectal and one bladder laceration and two cases of hemorrhage requiring transfusion) (Shull et al. 1993; Meeks et al. 1994).

Retrospective reviews have shown that iliococcygeus fascial suspension is similar in outcomes to abdominal procedures and sacrospinous ligament fixation (Barber and Maher 2013). However, there are no randomized trials that evaluate this technique.

17 Abdominal Approach to Apical Prolapse

17.1 Sacral Colpopexy

Sacral colpopexy has been shown to be effective and durable for the correction of apical prolapse. Traditionally, sacral colpopexy is performed via laparotomy; however, laparoscopic and robotic approaches are also commonly used.

Regardless of approach, the basic steps of the procedure stay the same (Fig. 17). The peritoneal cavity is entered, and if indicated, hysterectomy is performed and the cuff is closed. The vagina is elevated using a sponge stick, probe, or end-to-end anastomosis sizer. The bladder is dissected off of the anterior vagina. Attention is then turned to the posterior vagina, and the peritoneum over the posterior wall is incised and dissected off of the vaginal tissue for several centimeters on either side. The mesh is trimmed to fit the anterior and posterior vaginal walls and transfixed using three to six stitches of nonabsorbable suture. Sutures are placed full thickness through the fibromuscular layer of the vagina, but not through the vaginal epithelium. The mesh is placed such that it reaches approximately two-thirds of the way down the

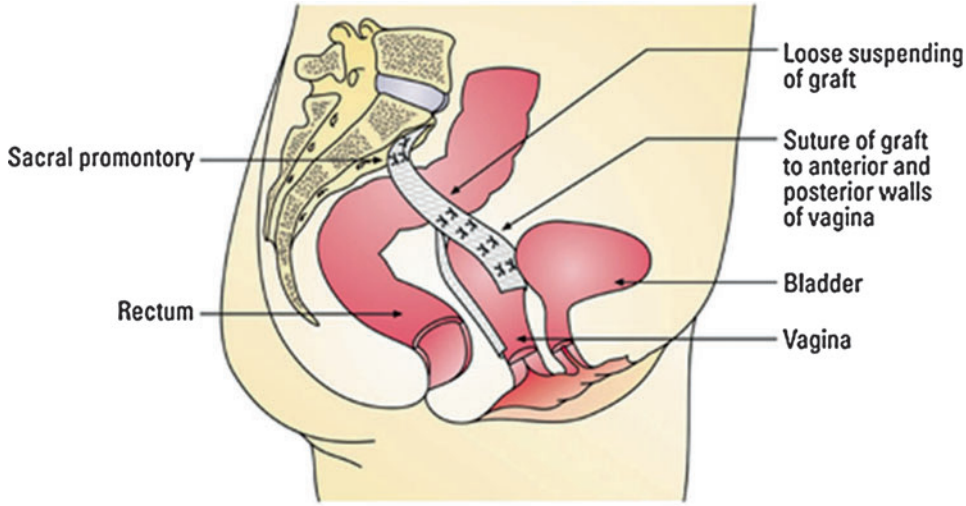

Fig. 17 Abdominal sacral colpopexy. The vaginal cuff is fixed to the anterior longitudinal ligament over the sacral promontory, using a piece of mesh or graft (Originally published in Cvach K, Dwyer P. Surgical management of pelvic organ prolapse: abdominal and vaginal approaches. World J Urol 2011;30(4):471–7; with kind permission of Springer Science+Business Media. All Rights Reserved)

anterior vagina, and a separate piece is placed at least halfway down the posterior vaginal wall. The two meshes are then sutured together above the cuff. The cul-de-sac is then obliterated using a Halban or Moschcowitz procedure.

Attention is then turned to the sacral promontory. The sigmoid colon, right ureter, aortic bifurcation, and common iliac vessels should be identified. The peritoneum over the sacral promontory is incised longitudinally and the underlying fatty tissue dissected off of the promontory. The middle sacral artery and vein should be identified at this step. The mesh is then transfixed to the anterior longitudinal ligament using two to three stitches of nonabsorbable suture. The mesh should be tensioned to avoid undue traction on the vagina. The peritoneum is then closed over the mesh.

Additional procedures at the time of sacral colpopexy may be indicated. A large randomized controlled trial showed that the addition of Burch urethropexy at the time of open sacral colpopexy reduced the rate of postoperative stress incontinence at 2 years from 57% to 37% in women who did not have stress incontinence preoperatively (Brubaker et al. 2008). As apical prolapse rarely occurs in isolation, repair of posterior prolapse may also be indicated at the time of colpopexy.

Outcomes and Complications

The success rate of abdominal sacral colpopexy for apical suspension ranges from 78% to 100% (Barber and Maher 2013). Over time, anatomic and subjective success rates tend to decrease, as prolapse tends to recur between 2 and 7 years (Nygaard et al. 2013). Severe intraoperative complications specific to colpopexy are rare and include hemorrhage from the sacral vascular plexus; complications from laparotomy may include enterotomy, ureteral damage, cystotomy, and wound infections.

The most common long-term complications after sacral colpopexy include recurrent prolapse, de novo stress incontinence, and mesh exposure. The median reoperation rates are 4.4% for recurrent prolapse, 4.9% for postoperative stress incontinence, and 3.4–5.1% for mesh exposure (Nygaard et al. 2004, 2013).

Abdominal Uterosacral Ligament Suspension

The abdominal approach to the uterosacral ligament suspension involves the same principles as the vaginal approach as described previously. The remnants of the uterosacral ligament are identified

and tagged at the level of the ischial spines. The ureters are identified, and the uterosacral ligaments are fixed to the vaginal cuff using permanent or delayed absorbable sutures.

17.2 Obliterative Procedures

All of the above procedures focus on reconstructing the vagina. An alternative approach is to obliterate the vagina. This approach may be considered in women who are no longer sexually active and do not have plans to have vaginal intercourse in the future. Obliterative procedures may be performed for post-hysterectomy vault prolapse or for uterovaginal prolapse (colpectomy/colpocleisis). The uterus may be left in situ (LeFort colpocleisis) or removed. Even with removal of the uterus, these procedures offer a relatively quick operative time, low risk of morbidity, and high rate of success.

17.3 Technique/Considerations

As these procedures are generally performed on older women with multiple comorbidities, the focus of the preoperative evaluation should be on optimization of their functional status and control of their comorbidities. These patients should be carefully counseled on the procedure and the permanent loss of access to the vagina for sexual function. When the uterus is to be left in situ, these patients should be carefully screened for risk factors for endometrial and cervical pathology. They should be screened for postmenopausal vaginal bleeding and consider a pelvic ultrasound to evaluate the endometrium. Cervical cytologic screening should be up to date and negative.

17.4 Total Colpectomy/Colpocleisis

Total colpocleisis refers to the removal of the vaginal epithelium (Fig. 18) within the hymenal ring posteriorly to within 0.5–2 cm of the external urethral meatus anteriorly (FitzGerald et al. 2006). Generally, the vaginal tissue is grasped and everted. The vaginal epithelium is excised in strips from the underlying vaginal muscularis. The muscularis is then inverted using a series of purse-string stitches. Once the prolapse is reduced, an aggressive perineorrhaphy and/or levator plication is performed. The anterior and posterior epithelia are sutured together with closure of the vagina.

17.5 Partial/LeFort Colpocleisis

A partial colpocleisis refers to when portions of the vaginal epithelium are left in place (Fig. 19). The LeFort modification is when the uterus is left in situ, and the epithelium is reconstructed in a manner to leave channels, through which vaginal discharge or blood can escape. The procedure is started by grasping the cervix and applying gentle traction. Rectangle sections are marked on the anterior and posterior vaginal walls; these are the areas to be denuded. The uterus is then reduced, and the cut edges of the remaining epithelium above and below the cervix are sewn together using interrupted sutures, such that the epithelium is inverted and it creates a tunnel in front of the cervix. A urinary catheter may be placed in this tunnel to ensure it is adequate and patent. The plication sutures are then continued laterally on either side to create lateral channels. As these sutures are placed, the prolapse is gradually reduced until it is entirely within the body. The final sutures may be placed at the level of the hymenal ring. The anterior and posterior epithelia are then reapproximated, using care to leave the lateral channels open. As above, an aggressive perineorrhaphy and levator plication are often performed to augment this repair (Evans et al. 2015).

Multiple studies have shown low rates of prolapse recurrence, high rates of patient satisfaction, and low rates of regret in appropriately counseled patients. Major complications of these procedures tend to be related to the performance of procedures on the elderly (cardiac, pulmonary, and cerebrovascular complications) and occur at a rate of

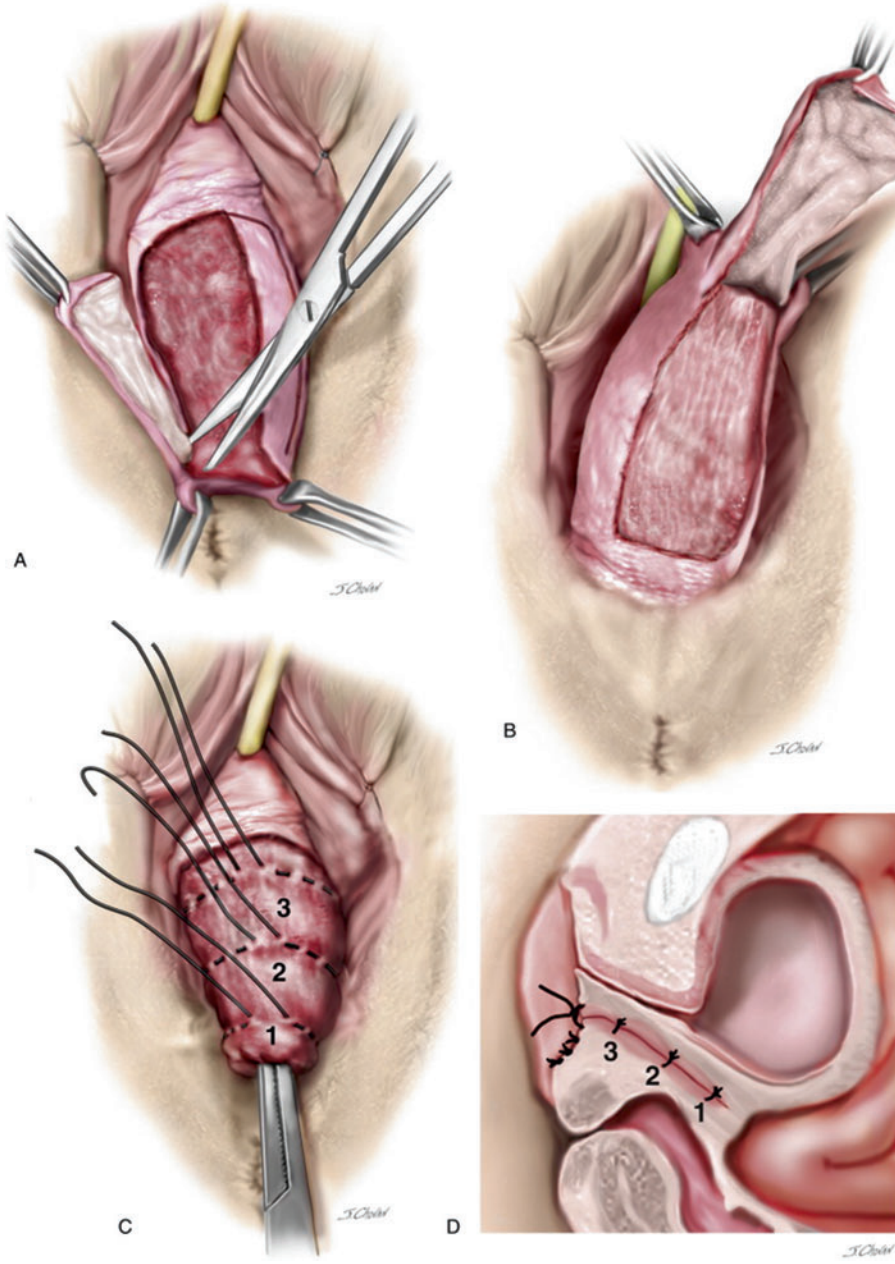

Fig. 18 Total colpectomy/colpocleisis. (**a**, **b**) The vagina is circumscribed and marked into quadrants. Each quadrant is removed by sharp dissection. (**c**) Purse-string sutures are placed; the leading edge is inverted by the tip of the forceps. Purse-string sutures are tied 1 before 2 and 2 before 3, with progressive inversion of the tissue. (**d**) The final relationship is shown in cross section (Reprinted from Urogynecology and reconstructive pelvic surgery, 4th Edition, Evans J, Silva WA, Karram MM. Obliterative procedures for pelvic organ prolapse, p400–410 (2015); with kind permission from Elsevier)

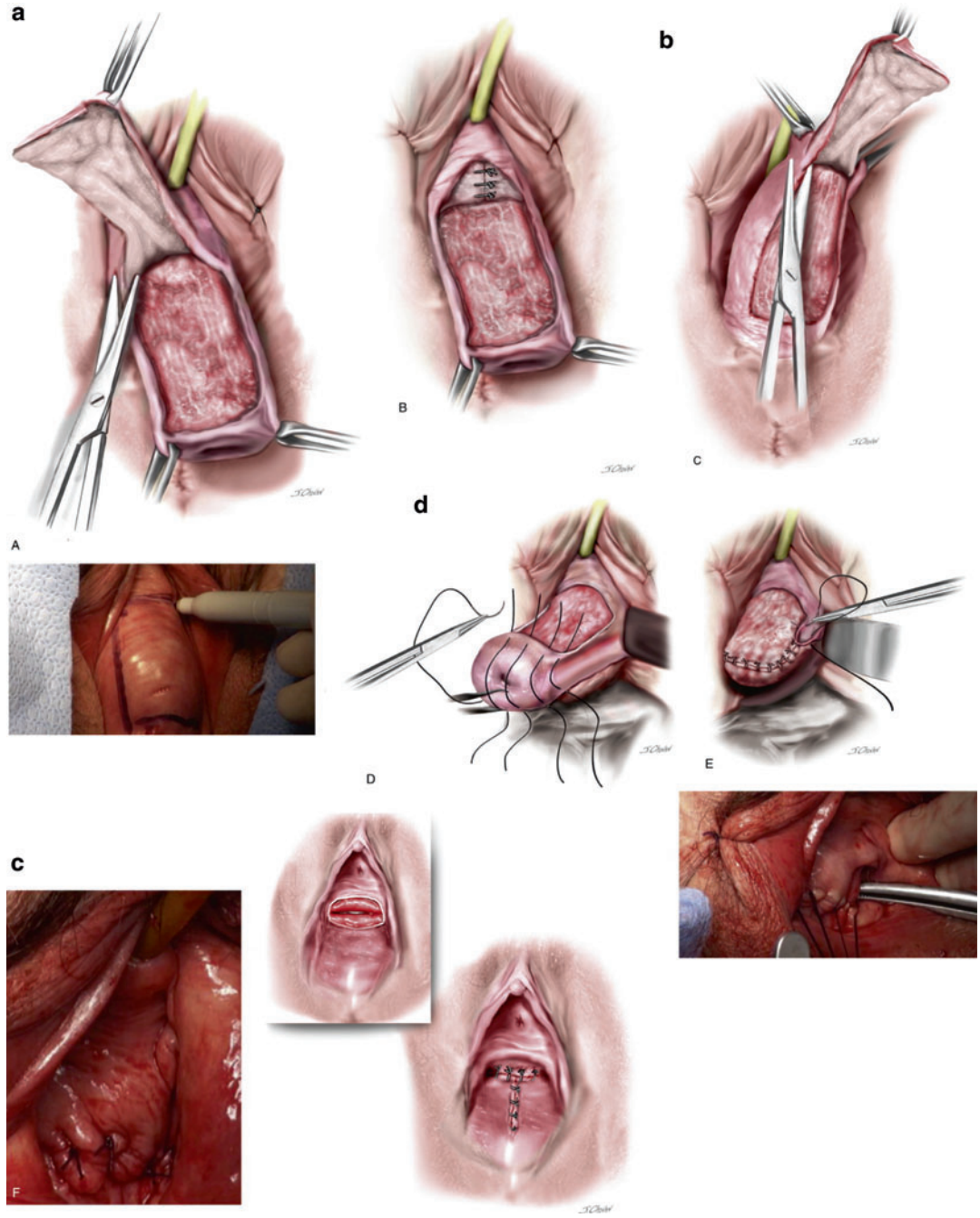

Fig. 19 LeFort colpocleisis. (**a**) A rectangular piece of the vagina has been removed. (**b**) A similar rectangular piece of the posterior vagina has been removed. (**c**) The cut edge of the interior incision is sewn to the distal cut edge of the posterior incision. Once the cervix is inverted, the sutures are continued up the lateral edges of the incisions on either side. (**d**) The entire vagina is inverted and the proximal incisions are sewn together horizontally. Note: draining channels are left in the lateral portions of the vagina to allow drainage of cervical discharge or uterine bleeding (Reprinted from Urogynecology and reconstructive pelvic surgery, 4th Edition, Evans J, Silva WA, Karram MM. Obliterative procedures for pelvic organ prolapse, p400–410 (2015); with kind permission from Elsevier)

approximately 2% (FitzGerald et al. 2006). Specific complications of the procedure include hemorrhage and pyelonephritis and appear at a rate of about 4%.

18 Posterior Prolapse

Women with symptomatic pelvic organ prolapse often have defects of the posterior vaginal wall. One study found that in women undergoing surgery for prolapse, 40% had posterior vaginal wall defects (Olsen et al. 1997). The posterior vaginal wall must usually be addressed separately from an anterior or apical suspension.

18.1 Technique

The traditional repair for posterior vaginal wall defects is the posterior colporrhaphy (Fig. 20). Two Allis clamps are placed on the perineum, which is then incised in a transverse fashion. If a perineorrhaphy is to be included, an inverted triangle of the skin is removed from the perineal body. The posterior vaginal wall is placed on gentle tension, and the vaginal epithelium is undermined using the Metzenbaum scissors up to the apex of the rectocele. The edges of the incision are grasped, and the epithelium is dissected off the underlying rectovaginal fascia bilaterally to expose the lateral attachments to the levator ani muscles. At this point, a traditional midline plication or a site-specific repair may be performed.

18.1.1 Midline Plication

The rectovaginal fascia is plicated in the midline with interrupted sutures, starting proximally and progressing toward the hymenal ring. Placement of these sutures should incorporate good purchase of the fibromuscularis and should be placed close to the junction with the epithelium to avoid injury to the rectum. The redundant vaginal epithelium is trimmed and the incision closed in a running, locked fashion. The caliber of the vagina at the end of the procedure should allow three fingerbreadths to fit comfortably.

18.1.2 Site-Specific Repair

The operator finger is placed in the rectum, and specific, palpable, or visual defects are repaired using interrupted, delayed, absorbable sutures (Fig. 21). If diffuse attenuation of the fascia is identified, a site-specific repair may not be technically feasible, and a midline plication is preferred. The redundant vaginal epithelium is trimmed and the incision closed in a running, locked fashion.

18.1.3 Graft or Mesh Augmentation

A posterior colporrhaphy may be augmented using graft or mesh. The material is cut to fit the space and sewn with permanent suture to the rectovaginal fascia at the level of the attachment to the levator ani muscles on either side. If the patient is undergoing a concomitant apical suspension, the graft may be fixed to the apical support sutures. The distal end is sutured to the perineum using absorbable sutures. The epithelium is then closed over the graft or mesh.

18.2 Outcomes and Complications

Traditional midline plication has success rates ranging from 76% to 97%. The most common complication of posterior colporrhaphy is dyspareunia. Postoperative dyspareunia is found in 11–27% after traditional posterior colporrhaphy, with de novo dyspareunia reported in 4–16% (Arnold et al. 1990; Lopez et al. 2001; Mellgren et al. 1995; Maher 2004). A three-way randomized controlled trial comparing traditional colporrhaphy to site-specific repair to porcine-derived graft showed that traditional colporrhaphy and site-specific repair had similar anatomic and functional outcomes. Porcine-derived graft augmentation resulted in improvement in symptoms similar to the other methods, but graft augmentation had significantly greater anatomic failures than the other two techniques (Paraiso et al. 2006). Graft augmentation may be considered in selected patients who have failed primary native tissue repair, with adequate preoperative counseling.

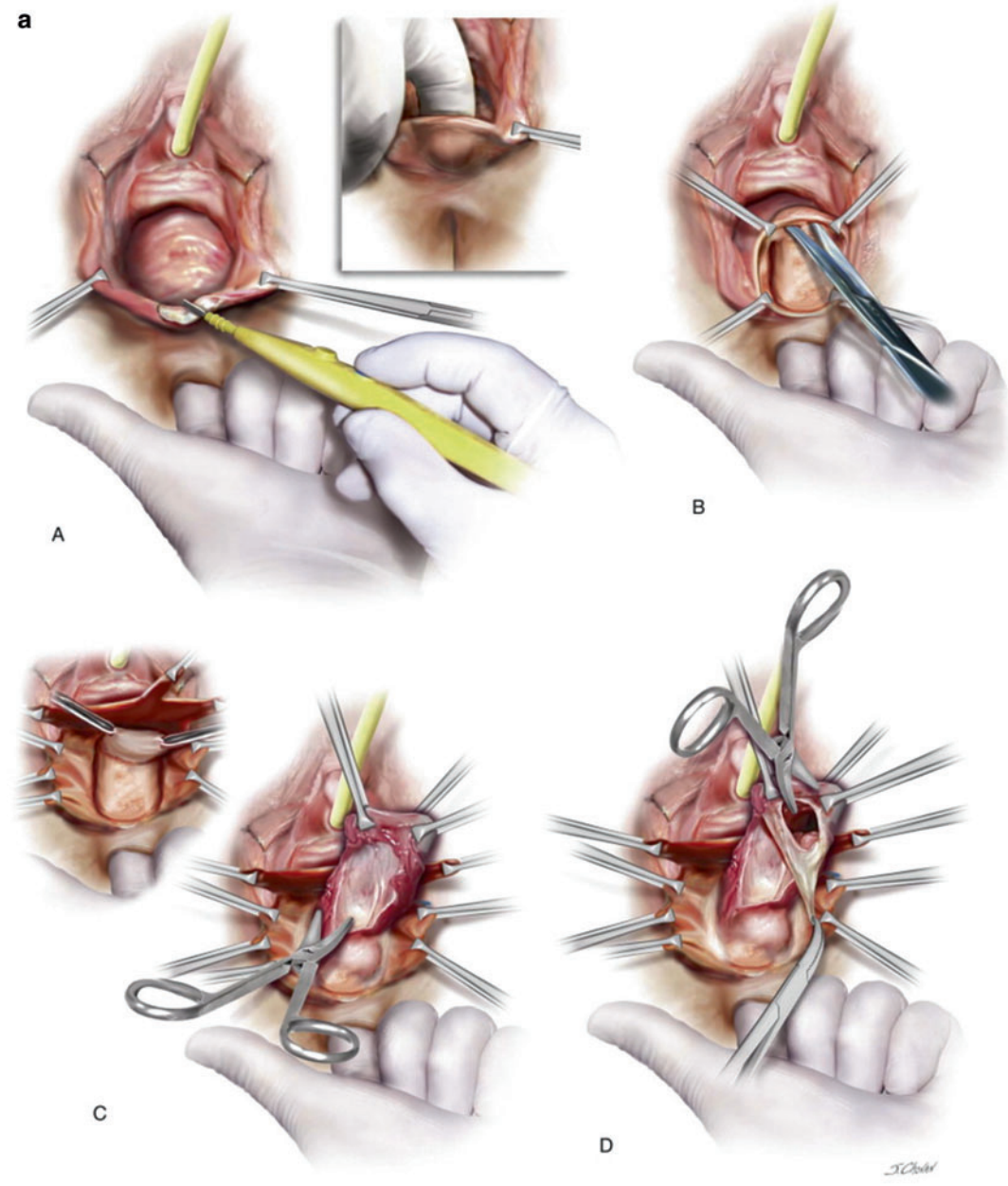

Fig. 20 (continued)

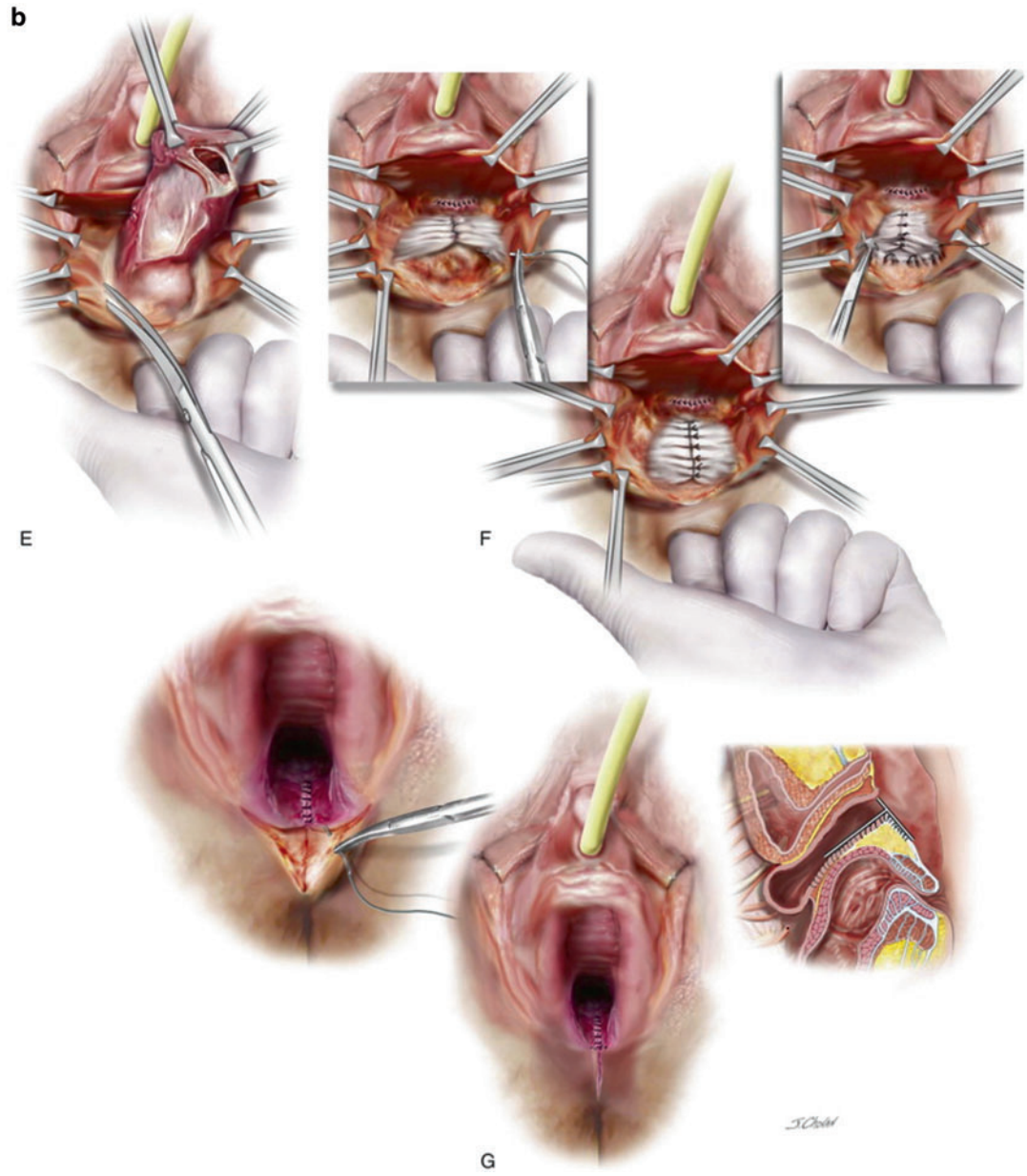

Fig. 20 Traditional posterior colporrhaphy. (**a**) The perineal skin is incised in the midline. (**b**) The posterior vaginal epithelium is mobilized off the rectum. (**c**, **d**) The enterocele sac is mobilized and entered. (**e**) The enterocele sac is excised or reduced, and the fibromuscular layer of the vagina is plicated in the midline. (**f**) A second layer may be plicated across the midline. (**g**) Perineorrhaphy is performed (Reprinted from Surgical Management of Pelvic Organ Prolapse, 1st Edition, Karram M. Surgical Correction of posterior pelvic floor defects, p139–164; with kind permission from Elsevier)

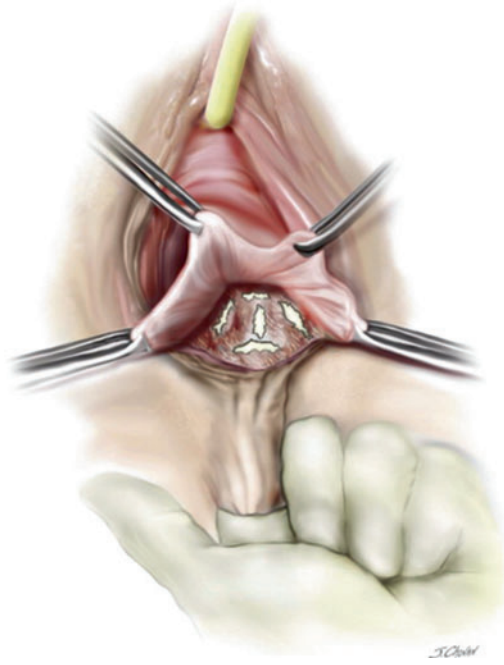

Fig. 21 Site-specific posterior defect repair. With finger in the rectum, discrete defects in the fibromuscular layer are identified. These defects are subsequently repaired using interrupted sutures (Reprinted from Surgical Management of Pelvic Organ Prolapse, 1st Edition, Karram M. Surgical Correction of posterior pelvic floor defects, p139–164; with kind permission from Elsevier)

19 Conclusion

Pelvic organ prolapse is a common problem that affects the daily activities for millions of women. The sensation of bulge in the vagina can be easily assessed and characterized by pelvic examination. Many patients may elect for expectant management or conservative management with a pessary. Radiologic testing is rarely indicated, and ancillary urodynamic testing may be indicated if the patient desires surgical intervention. Surgical treatment of prolapse is highly varied and depends greatly on the location of the prolapse, the degree of prolapse, and the patients' comorbidities and preferences. Surgical procedures are generally safe and well tolerated. Procedural success rates are hard to interpret, as success is generally considered anatomic success, symptomatic success, and absence of reoperation.

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Urinary Incontinence: Diagnosis, Treatment, and Avoiding Complications

Renee Rolston, and Begüm Özel,

Abstract

Urinary incontinence is defined as the complaint of involuntary leakage of urine. Urinary incontinence impacts physical, psychological, and social well-being. In order to achieve an accurate diagnosis, a detailed history and physical exam are important. An initial evaluation should include a detailed history, urinalysis, cough stress test, evaluation of post-void residual, focused neurologic assessment, and examination for urethral hypermobility and pelvic organ prolapse. Urodynamic testing and cystoscopy may be indicated in some patients. Treatment varies based on the type of urinary incontinence and symptom severity. First-line therapy should always consist of less invasive and more conservative treatment options as they have been shown to be highly effective with minimal risk. These therapies include pelvic floor exercises, biofeedback, bladder training, weight loss, modification in fluid and caffeine intake, urethral inserts, and incontinence pessaries. Depending on the type of incontinence characterized, more invasive treatment options can be implemented if no improvement with conservative management. Typically, women with stress incontinence who have failed conservative therapies are offered surgical intervention, whereas women with urgency incontinence may be treated with pharmacologic management, intradetrusor onabotulinum toxin A, or neuromodulation. Most incontinence can be made better with available therapies.

Keywords

Stress urinary incontinence • Urgency urinary incontinence • Mixed urinary incontinence • Sling

Contents

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1 Introduction

Urinary incontinence is defined as the complaint of involuntary leakage of urine (Haylen et al. 2010). The prevalence of urinary incontinence is estimated to range from 12% to 55% depending on the population studied (Castro et al. 2015). Urinary incontinence has been reported to affect up to 75% of older women (ACOG 2015). Urinary incontinence is associated with both depression and anxiety in women who are affected (Felde et al. 2016) and can lead to decrease in quality of life and negative impact on sexual function (Lim et al. 2016).

2 Diagnosis and Evaluation

2.1 History

History is a key part of the evaluation of urinary incontinence, and careful attention should be made to understanding the patient's complaints (Komesu et al 2016). History should include duration of incontinence, precipitating events, severity, frequency of occurrence, the presence or absence of nocturia, daytime urinary frequency, hesitancy or dysuria, fluid intake, daily pad use, and interference with activities of daily living (Haylen et al. 2010). The history obtained can be used to characterize and classify the type of incontinence or to identify underlying conditions that may cause incontinence. Tools that can be utilized to aide in obtaining a detailed history include a bladder diary and validated questionnaires such as the urogenital distress inventory, incontinence impact questionnaire, questionnaire for urinary incontinence diagnosis, incontinence quality for life questionnaire, and incontinence severity index (Staskin et al. 2005). When completing a bladder diary, patients are asked to record the timing and amount of fluid intake, voids and voided volumes, leakage episodes, and activity during leakage for 24–72-h period. As part of the history, medications should be reviewed to determine whether any of them might be contributing to urinary symptoms, such as diuretics, caffeine, alcohol, narcotic analgesics, anticholinergic drugs, antihistamines, psychotropic drugs, alpha-adrenergic blockers, alpha-adrenergic agonists, and calcium channel blockers (ACOG 2015).

2.2 Physical

Physical exam should include a pelvic exam, including evaluating for prolapse and an assessment of urethral mobility. When performing the pelvic exam, it is important to evaluate for pelvic organ prolapse and to exclude the presence of a urethral and/or pelvic mass. A urethral mass such as a diverticulum or pelvic masses such as fibroids may cause symptoms of urinary incontinence. As part of the pelvic exam, a speculum exam should be performed to evaluate for extraurethral urinary leakage which can occur if a fistula is present. A cough stress test during the pelvic exam, when positive, may confirm stress incontinence. The Q-tip or cotton-tipped swab test is a simple test to evaluate urethral hypermobility. Urethral hypermobility does not have an official definition from the International Continence Society/International Urogynecologic Association, but it can be defined as a resting angle or displacement angle of the urethra–bladder neck with maximum Valsalva of at least 30 degrees from the horizontal (Zyczynski et al. 2007). In the absence of prior anti-incontinence surgery, when point Aa is −1 or greater on the Pelvic Organ Prolapse Quantification Scale, nearly all patients demonstrate urethral hypermobility, and a Q-tip test may be deferred in these patients (Cogan et al. 2002).

During the initial evaluation of all women with incontinence, a focused neurologic examination is indicated, including assessment of gait, sensation

over the perineum and perianal skin, and evaluation for sacral reflexes. A detailed neurologic examination is not necessary unless there is presence of sudden onset incontinence or new onset of neurologic symptoms. A simple test for the sacral reflexes is the anal wink in which the skin near the anus is stroked lightly with a soft cotton-tipped swab. A reflex contraction of the anus should be seen. However, the reflex can be absent in some neurologically intact women.

2.3 Additional Testing

Before initiating further therapy, it is recommended to check a urinalysis to evaluate for urinary tract infection and hematuria; a urine culture may be performed if indicated. It may be necessary to check a post-void residual (PVR) via straight catheterization or bladder ultrasound to rule out retention and overflow incontinence in women with symptoms of incomplete bladder emptying or difficulty voiding, or in women with risk factors such as neurologic disease or diabetes mellitus. A PVR volume less than 50 mL is considered indicative of adequate bladder emptying (Haylen et al. 2010), and a PVR volume greater than 200 mL is considered indicative of inadequate emptying (Gehrich et al. 2007). An isolated finding of a raised PVR requires confirmation before being considered significant.

2.4 Urodynamics

Cystometry is a graphic depiction of bladder and abdominal pressure relative to fluid volume during filling, storage, and voiding. The information obtained during cystometry can be used to assess bladder sensation, capacity, and compliance and to determine the presence and magnitude of voluntary and involuntary detrusor contractions. Uroflowmetry and pressure-flow studies measure the rate of urine flow and the mechanism of bladder emptying (Walters and Karram 2015). Urethral pressure profiles and Valsalva leak point pressures can also be measured to make the diagnosis of urodynamic intrinsic sphincter deficiency. Studies have suggested that low urethral pressure measurements may be associated with poorer continence outcomes; a reliable cutoff measure to accurately predict surgical failure has not been found (Lim et al. 2016). Although Valsalva leak point pressures have been found to be weakly associated with subjective measures of incontinence severity, they have not been able to reliably predict surgical outcomes. Neuromuscular activity of the pelvic muscles and urethral sphincter during voiding can also be assessed during cystometry by using electromyography. The main role of electromyography is detecting coordination between detrusor muscle contraction and simultaneous urethral sphincter relaxation (Haylen et al. 2010).

Urodynamic testing should be used to evaluate patients with complicated urinary symptoms and inability to elicit evidence of stress urinary incontinence of cough stress test or to evaluate for occult stress incontinence in patients with pelvic organ prolapse. A multicenter randomized controlled study has demonstrated that for women with uncomplicated, demonstrable stress urinary incontinence, preoperative office evaluation alone was not inferior to evaluation with urodynamic testing for outcomes at 1 year; uncomplicated stress incontinence was defined as women with predominantly stress incontinence symptoms, negative urinalysis, PVR < 150 ml, the presence of urethral hypermobility, no history of pelvic irradiation, recent pelvic surgery, or significant prolapse (Nager et al. 2012).

When evaluating for urinary incontinence, cystourethroscopy is not routinely indicated. It should be considered in the setting of hematuria, acute-onset or refractory urgency incontinence, recurrent urinary tract infections, and suspicion for fistula or foreign body after gynecologic surgery.

3 Stress Incontinence

Stress urinary incontinence (SUI) is the complaint of involuntary leakage of urine on effort or exertion or on sneezing or coughing (Haylen et al.

2010). Stress incontinence is the most common type of incontinence in younger women.

Risk factors are not well known but are believed to be attributable to age, obesity, menopause and the loss of circulating estrogen, straining when evacuating the bowels, childbirth including the number of pregnancies, vaginal delivery, and operative vaginal delivery (McIntosh et al. 2015).

A basic office evaluation as described above has been shown to be a sufficient preoperative workup for a patient with uncomplicated SUI (Nager et al. 2012).

3.1 Pathophysiology/Anatomy

The proposed mechanisms of stress urinary incontinence are urethral hypermobility and intrinsic sphincter deficiency. It is theorized that urethral hypermobility is caused by insufficient support of the pelvic floor musculature and vaginal connective tissue to the urethra and bladder neck. This causes the urethra and bladder neck to lose the ability to completely close against the anterior vaginal wall with increases in intra-abdominal pressure leading to incontinence. Treatments for hypermobility stress incontinence are aimed at providing a backboard of support for the urethra.

Intrinsic sphincter deficiency (ISD) is attributed to a loss of urethral tone that normally keeps the urethra closed. This can occur in the presence or absence of urethral hypermobility and typically results in severe urinary leakage even with minimal increases in abdominal pressure. Urodynamic ISD is defined as a maximum urethral closure pressure of $\leq$20 cm H2O and/or abdominal/Valsalva leak point pressure $\leq$60 cm H2O (Lim et al. 2016). In general, ISD results from neuromuscular damage and can be seen in women who have had multiple pelvic or incontinence surgeries. Patients with ISD can be challenging to treat and tend to have worse surgical outcomes (Lukacz 2016).

3.2 Treatment

3.2.1 Conservative

Behavioral Modifications

First-line treatment for stress incontinence includes behavioral and lifestyle modifications. Depending on symptom severity, treatment with these conservative therapies should be tried for at least 6 weeks before considering subsequent therapies (Lukacz 2016). Implementation of dietary changes in which the consumption of beverages that exacerbate incontinence such as alcohol, as well as caffeinated and carbonated beverages, is reduced may be helpful. It is also advisable for women to normalize fluid intake if they are drinking >64 oz. of fluid/day. Another behavioral modification is the management of constipation; constipation can exacerbate urinary incontinence and increase risk of urinary retention. Obesity is a known risk factor for urinary incontinence, and weight loss in obese women has been shown to reduce urinary incontinence in multiple well-designed studies (Vissers et al. 2014; Wing et al. 2010).

3.3 Pelvic Floor Muscle Training (PFMT)

In addition to behavioral and lifestyle modifications, pelvic floor muscle training is also grouped with conservative first-line treatment for SUI and has been shown to be very effective in treating stress incontinence. The Cochrane Review found that in 18 studies, there was high-quality evidence that PFMT is associated with cure of stress incontinence (RR, 8.38; 95% CI, 3.68–19.07) and moderate-quality evidence of cure or improvement of stress incontinence (RR, 17.33; 95% CI, 4.31–69.64) (Dumoulin et al. 2015).

Pelvic muscle exercises, also called Kegel exercises, aim to strengthen the pelvic floor musculature to provide a backboard for the urethra and reflexively inhibit detrusor contractions. When performing pelvic muscle exercises, different regimens have been prescribed. One simple

instruction is to tell the patient to contract her pelvic floor using the same muscles they would use to stop urine flow or gas. The basic regimen consists of three sets of 8–12 contractions sustained for 8–10 s each, performed three times a day.

3.4 Incontinence Pessary

Incontinence pessary restores continence by stabilizing the proximal urethra and urethrovesical junction. Incontinence pessaries are thought to improve urinary incontinence in some women by increasing urethral functional length, urethral closure pressures, and cough profiles (McIntosh et al. 2015). The knob of the incontinence pessary should be placed at or below the bladder neck in order to stabilize the posterior urethra (McIntosh et al. 2015). A randomized controlled trial comparing the use of behavioral therapy alone (including pelvic floor muscle training), pessary alone, and combined behavioral therapy and pessary found that at 3 months pessaries were not as effective as behavioral therapy based in patient satisfaction. Therefore, although incontinence pessaries are a treatment option, they are not first line given the effectiveness of pelvic muscle exercise (Richter et al. 2010).

3.5 Urethral Inserts

A urethral insert is an occlusive device that acts as a mechanical barrier to prevent urinary leakage by sealing the urethral lumen (Sirls et al. 2002). They are self-inserted and designed for single use. The only urethral insert currently available for use is the FemSoft (Rochester Medical, Stewartville, MN). The most common side effects are urethral discomfort, hematuria, urinary tract infections, and bladder irritation. Contraindications for the use of urethral inserts include pregnancy, significant urge incontinence and unstable bladder contractions, neuropathic bladder, a history of recurrent bladder infections, the use of anticoagulants, and inflammatory or malignant lesions of the lower urinary tract.

3.6 Surgery

Stress urinary incontinence should be demonstrated objectively before any surgery is performed. This can be done with a cough stress test or with simple or multichannel urodynamic testing. A positive cough stress test is the visualization of fluid loss from the urethra simultaneously with a cough. This test should be performed with a full bladder in the supine and/or standing position. If the cough stress test is negative and patient reports symptoms of SUI, it is appropriate to perform urodynamic testing as next step. Once stress incontinence is objectively identified, surgical options include mid-urethral sling, pubovaginal sling, and Burch colposuspension. The most common surgical intervention for SUI is the mid-urethral sling procedure (Lim and Swyer 2009).

3.7 Mid-urethral Sling (MUS)

The first commercially available mid-urethral sling (MUS) was the tension-free vaginal tape (TVT) (Gynecare, Ethicon Women's Health and Urology, Somerville, New Jersey, USA), first described by Ulmsten in 1996 (Ulmsten et al. 1996) and introduced into the US market in 1998. According to the American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), the polypropylene mesh is considered the standard of care in the surgical treatment of SUI. There are two types of mid-urethral slings the retropubic sling and the transobturator (TOT) sling. Mid-urethral slings function by providing a backboard for the urethra, facilitating compression of the mid-urethra when intra-abdominal pressure increases.

When performing a retropubic MUS, a segment of synthetic material is inserted via the vagina and passed on each side of the urethra through the retropubic space through two exit incisions on the anterior abdominal wall. Once the sling is placed, position is assessed and confirmed to be tension-free. Absolute contraindications to the retropubic MUS include pregnancy,

active oral anticoagulation, and the presence of important structures in the path of the trocars or sling, which may include a pelvic kidney, vascular graft, and low ventral hernias. A retrospective study comparing retropubic MUS, transobturator tape (TOT), and pubovaginal sling in women with ISD showed that retropubic MUS and pubovaginal slings had similar cure rates – retropubic MUS (86.9%) versus pubovaginal sling (87.3%) (Jeon et al. 2008). Potential complications of retropubic slings include bladder perforation, pelvic visceral injuries, vascular injuries and hemorrhage, mesh exposure, de novo development of urgency and urge incontinence, bladder outlet obstruction, pelvic pain, and urinary tract infection.

3.8 Transobturator

In 2001, Delorme described the transobturator technique for mid-urethral sling placement which avoided going in the retropubic space and is associated with less bladder perforation and visceral and vascular injury (Delorme 2001). The TOT can be performed via inside out or outside in technique in which the entry/exit point is the medial border of the obturator foramen at the level of the clitoris. The needle passage avoids any significant passage through the space of Retzius and nearly eliminates the possibility of intraperitoneal passage. As a result, the risk of bladder injury is lower after the TOT compared to the retropubic sling (0.6 vs. 4.5%; RR 0.13, 95% CI 0.08–0.20). Major vascular or visceral injury and operative blood loss is also lower with the TOT sling (Ford et al. 2015).

Another important complication is voiding dysfunction, which is less common after the TOT sling compared to the retropubic sling (RR 0.53, 95% CI 0.43–0.65) (Ford 2015). Groin pain appears more frequently after the TOT sling (6.4 vs. 1.3%; RR 4.12, 95% CI 2.71–6.27), whereas suprapubic pain is less common after the TOT (0.8 vs. 2.9%; RR 0.29, 95% CI 0.11–0.78). There is no difference in rates of mesh exposure or extrusion (Ford et al. 2015).

One important study that compared the TOT sling with the retropubic sling was the trial of mid-urethral slings (TOMUS); this was a multicenter, randomized equivalence trial comparing outcomes with retropubic and TOT mid-urethral slings in women with stress incontinence (Richter et al. 2010). Objective and subjective outcomes at 12 months were similar between the two approaches, with objective outcome of about 80% for both groups. Clinically important complications included voiding dysfunction requiring surgery, the use of catheter, or both, which was seen in 2.7% in women who had the retropubic sling versus none of the women who had a TOT sling ($p = 0.004$) and neurologic symptoms, seen in 9.4% of women in the TOT sling versus 4% in the retropubic sling ($p = 0.01$). Overall, the lower risk of most complications seen with the TOT sling makes it an excellent option in appropriately selected patients; however, there is a higher rate groin pain and neurologic complications, which must be considered.

Indications for TOT sling placement are the same as for retropubic MUS with the exception of intrinsic sphincter deficiency. In women with either a maximum urethral closure pressure of 20 cm H_2O or less or a pressure rise from baseline required to cause incontinence (Δ Valsalva or cough leak point pressure) of 60 cm H_2O or less, the retropubic sling appears to be more effective. Of the 138 women randomized in one study, objective failure as defined as urodynamic stress incontinence at 6 months follow-up, 45% of women who had the TOT sling and 21% of women who had the retropubic sling had USI, and 13% of women in the TOT sling group went on to have another anti-incontinence procedure (Schierlitz et al. 2008).

3.9 Pubovaginal (Autologous Sling)

Autologous slings work by supporting the proximal urethra and bladder neck achieving continence by providing a direct compressive force on the urethra/bladder outlet. Long-term success is based on the healing and fibrosis of the sling

which passes through the endopelvic fascia. Autologous slings are placed at the bladder neck and are mainly reserved for women with severe stress urinary incontinence (SUI) and a non-mobile, fixed urethra, declining to have synthetic mesh implanted, recurrent SUI after a synthetic sling or history of a complication after a synthetic sling such as vaginal exposure or extrusion (Blaivas et al. 2013). It is also preferred to use an autologous sling in patients who have been irradiated, have had urethral injuries, and those who are undergoing either simultaneous or prior urethrovaginal fistula or diverticulum repair (Swierzewski and McGuire 1993). Compared to the mid-urethral sling, the pubovaginal sling is more invasive because it requires an abdominal incision to harvest fascia for the sling.

Complications of the pubovaginal sling include injury to the bladder and urethra, pelvic visceral injury, voiding dysfunction, superficial wound infection, seromas, and fascial hernias (Walters and Karram 2015).

In a meta-analysis, when compared to mid-urethral slings, the autologous sling is equally efficacious (RR 0.97 for incontinence at 12 months; 95% CI 0.78–1.20) but had longer operating time (mean difference 60 min; 5% CI 57–63 min), greater perioperative complications (RR, 1.59; 95% CI, 1.03–2.44), and greater de novo detrusor overactivity (RR, 3.21; 95% CI, 1.29–8.03) (Rehman et al. 2011). When compared to the Burch urethropexy, in a well-designed multicenter randomized trial, at 24 months of follow-up, success rates were found to be higher for women who had an autologous sling compared to the Burch urethropexy, but there were more urinary tract infections, difficulty voiding, and postoperative urgency incontinence after the autologous sling (Albo et al. 2007).

3.10 Retropubic Urethropexy

Retropubic procedures include the Burch colposuspension and the Marshall-Marchetti-Krantz (MMK) procedure. The MMK procedure is generally no longer performed but involved in the use of permanent suture to secure the paravaginal tissue to periosteum of pubic symphysis; a known complication is osteitis pubis, a painful, noninfectious inflammation of the pubic symphysis. The Burch colposuspension involves the use of suture to secure paravaginal tissue to Cooper's ligament. The Burch colposuspension requires a low transverse incision to assess the space of Retzius. Two delayed absorbable or non-absorbable sutures are placed through the pubocervical fascia; one is placed 2 cm lateral to the mid-urethra, and the other is 2 cm lateral to bladder wall at the level of the urethrovesical junction bilaterally. The suture is then passed through Cooper's ligament. With a hand in the vagina to elevate the pubocervical fascia, the sutures are tied down; a suture bridge is created. Healing occurs by fibrosis in the space of Retzius, and support for the urethra is created.

The Burch colposuspension can be utilized in patients with SUI undergoing a concomitant abdominal procedure or in women who decline the use of mesh. Studies comparing the Burch colposuspension to slings (both mid-urethral and autologous) show similar effectiveness at 12 months (RR, 1.24; 95% CI, 0.93–1.67) (Lapitan and Cody 2016). There is a lower risk of voiding dysfunction with the Burch colposuspension compared to slings (RR, 0.41; 95% CI, 0.26–0.67). There is no difference in overall risk of perioperative complications between the Burch urethropexy and the mid-urethral slings (RR, 1.11; 95% CI, 0.66–1.87). However, women undergoing open retropubic colposuspension were nearly twice at risk of developing new or recurrent prolapse compared to those undergoing sling procedures (33.9 vs. 20.1%; RR, 1.85; 95% CI, 1.25–2.75) (Lapitan and Cody 2016).

3.11 Urethral Bulking Agents

Urethral bulking agents consist of non-biodegradable and nonimmunologic material which is injected transurethral or periurethral into the periurethral tissue around the bladder

neck and proximal urethra to increase urethral resistance. Durasphere EXP (Carbon Medical Technologies, St. Paul, Minnesota, USA), Coaptite (Boston Scientific, Franksville, Wisconsin, USA), and Macroplastique (Cogentix Medical, Minnetonka, Minnesota, USA) are the bulking agents that are currently available.

The most common indications for urethral bulking agents include intrinsic sphincter deficiency with or without urethral hypermobility, persistent SUI after sling or urethropexy, and in women who cannot tolerate the risk of general anesthesia; other indications include women who cannot discontinue anticoagulation, are young and desire future fertility, and have SUI and poor bladder emptying (Cespedes and Serkin 2009). Urethral bulking agents have been shown to be less effective than surgery and usually require the need for repeat injections. Meta-analysis for the efficacy of Macroplastique found improvement rate of 75% (95% CI 69–81%) and cure/dry rates of 43% (95% CI 33–54%) at short-term follow-up (Ghoniem and Miller 2013). This is similar to success rates with other products (Reynolds and Dmochowski 2012). Managing patient expectations of outcome is important. Relative contraindications to the use of urethral bulking injections include active urinary tract infection, high post-void residual urine (>100 mL), urinary stricture/obstruction, severe detrusor overactivity, and fragile urethral mucosa. If no relief after two or three injections, further injections should not be attempted (Walters and Karram 2015).

4 Urgency Incontinence

Urgency urinary incontinence (UUI) is the complaint of involuntary urine leakage associated with urgency defined as the complaint of sudden compelling desire to pass urine that is difficult to defer, and overactive bladder (OAB) is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathologies (Haylen et al. 2010). UUI is more common in older women and may be associated with comorbid conditions that occur with age. It is believed to result from detrusor overactivity, leading to involuntary detrusor muscle contractions during bladder filling (Lukacz 2016).

> The American Urological Association has identified behavioral therapy as the first-line treatment option and pharmacologic treatment as the second-line treatment option for nonneurogenic OAB in adults.

In patients with UUI refractory to behavioral and pharmacologic management, sacral nerve stimulation and intradetrusor injection of onabotulinum toxin A may be recommended (Singh et al. 2015).

4.1 Conservative

Pelvic floor exercises have been demonstrated to be effective in the treatment of UUI. They are more effective when combined with biofeedback or verbal feedback. Weight loss with diet and exercise, caffeine reduction, and 25–50% reduction in fluid intake gave all been demonstrated to be efficacious and should comprise the initial management (Olivera et al. 2016).

Bladder training has been shown to be effective for women with urgency incontinence. Bladder training starts with timed voiding. Patients should keep a voiding diary to identify their shortest voiding interval. Patients are instructed to void by the clock at regular intervals based on the shortest time interval identified between voids in voiding diary. Urgency between voiding is controlled with either distraction or relaxation techniques. When the patient can go two days without leakage, the time between scheduled voids is increased. The intervals are gradually increased until the patient is voiding every 3–4 h without urinary incontinence or frequent urgency. Successful bladder training can take up to 6 weeks (Lukacz 2016).

4.2 Pharmacologic Management

If behavioral treatments fail, the next step is a trial of antimuscarinics. Antimuscarinics block the basal release of acetylcholine during bladder filling resulting in increasing bladder capacity and decreased urgency (Lukacz 2016). The currently available antimuscarinic drugs for the treatment of UUI and OAB are listed in Table 1. Treatment should be started at the lowest dose and titrated up if there is insufficient response in treatment and minimal side effects. Improvement in symptoms may take up to 4 weeks. A systematic review, including 23 studies, concluded that improvement with anticholinergics, either alone or combined with bladder training, is significantly greater than improvement with bladder training alone (Castro et al. 2015). Despite the effectiveness of antimuscarinics therapy, it has a low adherence rate secondary to their side effect profile including dry mouth, constipation, blurred vision for near objects, tachycardia, drowsiness, and decreased cognitive function.

Antimuscarinics are contraindicated in patients with gastric retention and untreated angle-closure glaucoma.

In patients that have contraindications to antimuscarinic or cannot tolerate antimuscarinics, β3-adrenergic agonist may be an option. The current β3 agonist on the market is mirabegron, and it has been shown to be effective in the management urgency. Mirabegron acts by promoting relaxation of the detrusor muscle and increasing the bladder capacity without increasing the residual volume (Castro et al. 2015). Patients with severe or uncontrolled hypertension should not be prescribed mirabegron.

Vaginal estrogen therapy is another medication used for treatment of either stress or urgency incontinence. Vaginal atrophy can lead to symptoms of urinary frequency and dysuria and can contribute to incontinence, and correction of vaginal atrophy with topical estrogen may improve urinary symptoms. Vaginal estrogen therapy can be in the form of a cream, ring, or tablet (Cody et al. 2012). Evidence suggests that vaginal estrogen therapy may improve continence (RR, 0.74; 95% CI, 0.64–0.86). There are 1–2 fewer voids in 24 h among women treated with vaginal estrogen, and there is less urgency and frequency (Cody et al. 2012).

4.3 Percutaneous Tibial Nerve Stimulation

Percutaneous tibial nerve stimulation (PTNS) delivers neuromodulation to the pelvic floor through the S2–4 junction of the sacral nerve plexus via the posterior tibial nerve. A 34-gauge needle electrode is inserted above the ankle, and the tibial nerve is accessed. This area has projections to the sacral nerve plexus, creating a feedback loop that modulates bladder innervation. Initial therapy consists of 12-weekly 30-min treatments (Gaziev et al. 2013). In a randomized trial of 220 adults, the 13-week subject global response assessment for overall bladder symptoms demonstrated statistically significant improvement in bladder symptoms from baseline with PTNS over sham therapy; 54.5% reported being moderately or markedly improved with PTNS compared to 20.9% of participants who received the sham therapy ($p < 0.001$) (Peters et al. 2010).

4.4 Intradetrusor Onabotulinum Toxin A

Onabotulinum toxin A blocks neuromuscular transmission by binding to receptor sites on nerve terminals and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings (Balchandra and Rogerso 2014). The most commonly recommended dose for nonneurogenic UUI/DO is BoNT-A 100 units. It is administered under cystoscopic visualization by evenly distributed intradetrusor injections across 20 sites approximately 1 cm apart, sparing the trigone of the bladder (Liao and Kuo 2015). Onabotulinum toxin A is indicated in urgency refractory to

Table 1 Antimuscarinic medications for treatment of women with urgency urinary incontinence or overactive bladder

Medication	Available formulations
Darifenacin	Extended release
Fesoterodine	Extended release
Oxybutynin	Immediate release Extended release Transdermal patch Transdermal gel
Solifenacin	Extended release
Tolterodine	Immediate release Extended release
Trospium	Immediate release Extended release

medical treatment. Contraindications include active infection, acute urinary retention, unwillingness or inability to self-catheterize, and known hypersensitivity to the toxin (Liao and Kuo 2015). In a large, randomized controlled trial of onabotulinum toxin A compared to placebo, at 12 weeks, onabotulinum toxin A significantly decreased urinary incontinence episodes per day (-2.95 vs. -1.03, $p < 0.001$), and reduction in all OAB symptoms as assessed by validated quality of life questionnaires was significantly greater with onabotulinum toxin A compared to placebo (Chapple et al. 2013). The need to self-catheterize occurred in 6.9% of participants, and urinary tract infections were seen in 20.4%, which was the most common complication seen (Chapple et al. 2013).

4.5 Sacral Neuromodulation

Sacral neuromodulation consists of the surgical implantation of electrodes in the S3 sacral nerve root and of an electric impulse generator, which is implanted in the subcutaneous tissue. It is reserved for severe cases of urgency refractory to conventional treatments. The mechanism of action is not fully understood, but electrical impulses are believed to act in both afferent and efferent fibers. The electrode implantation is performed in two stages in order to reduce complications and false-negative rates (Balchandra and Rogerso 2014). The first stage is the testing phase in which the electrode is implanted and positioned using radioscopy. The definitive implant is offered to patients who exhibit a positive response at least a 50% symptom improvement in the first stage after 1–4 weeks. Cure and improvement rates are 30–50% and 60–90%, respectively (Castro et al. 2015; Yamanishi et al. 2015). Complication rates are low and include adverse change in bowel habits, electrically induced discomfort, pain at the implantable pulse generator site, and infection (Olivera et al. 2016).

4.6 Mixed Urinary Incontinence

Mixed urinary incontinence is defined as the complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing. The pathophysiology is poorly understood. Initial treatment is conservative and should aim at treating both the SUI and UUI components. Subsequent therapy needs to be individualized to the patient's primary complaint and degree of bother from the SUI and UUI. Typically, outcomes with anti-incontinence surgery for women with MUI are poorer than women with SUI alone. Persistent DO after anti-incontinence surgeries is seen in up to 74% of women, typically leading to lower satisfaction with outcome of surgery (Bandukwala and Gousse 2015). Preoperative counseling on persistent UUI and DO after surgery is important when offering these women surgical treatment (Komesu et al. 2016).

5 Conclusion

Urinary incontinence is a treatable medical condition that significantly affects quality of life. A variety of conservative, pharmacologic, and interventional therapies exist to treat this condition.

6 Cross-References

- Avoiding Complications
- Minimally Invasive Procedures for Incontinence and Lower Urinary Tract Disorders: Indications
- Pelvic Organ Prolapse: Diagnosis
- Treatment and Avoiding Complications

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Diagnosis and Management of Delayed Postoperative Complications in Gynecology: Neuropathy, Wound Complications, Fistulae, Thromboembolism, Pelvic Organ Prolapse, and Cuff Complications

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Abstract

Surgical complications are an inevitable occurrence for any surgeon. Such complications may be a source of significant morbidity and even mortality. Delayed surgical complications typically present after the patient is discharged from the hospital. This chapter describes the presentation, evaluation, and management of the most common delayed postoperative complications. Delayed complications may be broadly categorized into those found in the early postoperative period and those in the later postoperative period. The first 2 weeks after surgery is a key time to evaluate and diagnose nerve injuries and wound complications, including infectious complications. Genital tract fistulae and thromboembolism may also present in this time period, but are also commonly seen in the first 3 months after surgery. Pelvic organ prolapse and cuff complications may present months to years after surgical intervention. The surgeon must be vigilant in the postoperative period for any sign of a delayed surgical complication, as prompt diagnosis and management is critical to minimize the effect upon the patient.

Keywords

Coagulation • Cuff complications • Fistula • Nerve injury • Postoperative • Prolapse • Thromboembolism • Wound

1 Introduction

Some of the most commonly performed surgical procedures are performed by obstetrician/gynecologists. Cesarean section and hysterectomies are among the most commonly performed major surgeries in the United States, accounting for 1.8 million procedures in 2010 alone (National Center for Health Statistics (NCHS) 2010). These procedures are generally safe; however, occasionally complications may occur. Surgical complications range in both severity and acuity. When injuries occur during surgery, they may be immediately repaired, often with minimal impact on the patient. Intraoperative injuries that are not recognized until the postoperative period generally have worse outcomes than those repaired at the time of surgery. In order to minimize the impact on patients, it is critical for any surgeon to promptly identify and appropriately manage any complications of these common surgical procedures.

2 Delayed Complications Presenting in the Immediate Postoperative Period (Within 2 Weeks)

2.1 Neurologic Injury

Neurologic injury complicates approximately 1–2 % of gynecological surgery. Many injuries are due to improper positioning or self-retaining retractors; however, direct surgical trauma, suture entrapment, or hematoma formation can also be involved (Bohrer et al. 2009; Warner et al. 2000). Symptoms almost always present soon after surgery, and, although most resolve completely with appropriate treatment, some patients continue to have long-term neurologic consequences. Therefore, prevention, early recognition, and treatment initiation are paramount.

Nerves that may be injured after pelvic surgery include: femoral, lateral femoral cutaneous, ilioinguinal, iliohypogastric, genitofemoral, common perineal, sciatic, and obturator.

2.2 Femoral Nerve

Femoral nerve (L2-L4) is the largest branch of the lumbar plexus that courses between the psoas and the iliacus muscles in the abdomen, then passes under the inguinal ligament, and enters the thigh. Gynecologic surgery and particularly the abdominal hysterectomy are the most frequent causes of iatrogenic injury to the femoral nerve.

Injury to the femoral nerve can occur throughout its course due to variable mechanisms. The most frequent cause is related to the use of self-retaining retractors. Retractor blades placed on the psoas muscle cause injury by compressing the nerve, particularly with the use of longer retractor blades. The retractor can also compress the nerve where it traverses the abdominal wall by lateral displacement of the psoas muscle.

To avoid such injury, the shortest retractor blades should be used, particularly in thin patients. Folded laparotomy sponges or towels can be placed between the retractor and the abdominal wall. Disposable retractors that don't use blades and therefore distribute the pressure evenly can be considered. The risk of injury is directly related to length of surgery.

Another mechanism of injury of the femoral nerve is patient positioning. In dorsal lithotomy position excessive hip flexion, external rotation or abduction can compress the nerve against the inguinal ligament. Close attention to proper positioning is imperative to decrease the risk of compression injury. Thighs should not be excessively abducted or externally rotated and hip flexion should not exceed 80–90°.

Although less common, injury can also occur due to direct transection, incorporation into a suture, or a hematoma causing nerve compression.

The classic presentation of postoperative femoral nerve injury is a patient who cannot climb stairs or falls when trying to get out of bed. The motor deficits include inability to flex the hip or extend the knee as well as an absent patellar reflex.

Sensory deficits usually involve paresthesia over the anterior-medial thigh and leg.

If a neurological injury is suspected after surgery, a thorough neurological examination may provide the diagnosis. Electromyography and nerve conduction studies may narrow down the location of injury. Imaging studies such as MRI, CT scan, or ultrasound can be used to detect formation of a hematoma or other fluid collections causing nerve compression.

After diagnosis, treatment should be initiated immediately. In cases of suspected transection or suturing, surgical reexploration and repair may be needed. Nerve compression from a hematoma can be relieved with drainage. Physical therapy should be initiated as soon as possible to prevent muscle atrophy. Knee stabilizers may be used to counteract thigh muscle weakness during standing.

Most patients will achieve full recovery, although time till recovery varies and may take up to several months (Bradshaw and Advincula 2010; Chan and Manetta 2002; Craig 2013; Irvin et al. 2004).

2.3 Lateral Femoral Cutaneous Nerve

Lateral femoral cutaneous nerve (L2-L3) courses over the iliacus muscle and passes under the inguinal ligament near the anterior superior iliac spine. Similarly to the femoral nerve, it is at risk of compression from excessive hip flexion in dorsal lithotomy position as well as with inappropriate placement of lateral retractor blades. Neurologic deficits associated with this nerve are loss of sensation, paresthesia, and pain over the anterior lateral thigh from the inguinal ligament to the knee, a condition sometimes referred to as **meralgia paresthetica** (Bradshaw and Advincula 2010; Craig 2013; Irvin et al. 2004).

2.4 Ilioinguinal and Iliohypogastric

Ilioinguinal (T12-L1) and iliohypogastric (T12-L1) nerves are frequently grouped together due to difficulty in distinguishing individual effects. The nerves run laterally through the head of the psoas muscle, pass diagonally along the anterior surface of quadratus lumborum, penetrate transversus abdominis, and enter the anterior abdominal wall. The nerves are susceptible to injury if a transverse abdominal incision is extended laterally, particularly beyond the edge of the rectus muscle at which point the edge of the

fascia is close to the nerve branches. Injury from trocar placement in laparoscopic surgery has also been reported.

The nerve damage typically occurs from direct surgical injury or nerve incorporation during fascial closure as well as scar formation after surgery. To decrease the risk of injury, the width of a transverse incision should be kept within the width of the rectus muscle. Neuropathy typically manifests with burning or pain at the incision site that radiates to the groin as well as paresthesia over mons pubis, labia, and inner thigh. The symptoms typically improve after infiltration with local anesthetic.

Treatment typically includes pharmacologic agents such as tricyclic antidepressants or gabapentin; however, nerves blocks, trigger point injection, or surgical nerve resection may also be necessary. Resecting the nerve requires extending the prior transverse incision to the anterior superior iliac spine and exposing the interface between the external oblique and the internal oblique muscle. The two nerves course between these two muscles and can be identified and sectioned close to the lateral sidewall.

Complete relief of pain can occur after nerve resection in more than 70 % of patients. Ilioinguinal and iliohypogastric nerve entrapment is typically under recognized and should be considered in cases of chronic pelvic pain associated with history of abdominal surgery (Bradshaw and Advincula 2010; Irvin et al. 2004).

2.5 Genitofemoral

The genitofemoral nerve (L1-L2) runs along the ventral surface of the psoas muscle, lies lateral to the external iliac artery, and branches near the inguinal ligament. Similarly to the femoral nerve, it is at risk of compression during laparotomy with the use of self-retaining retractors. In addition it can be directly damaged during retroperitoneal dissection, removal of pelvic masses adherent to the side wall, or with removal of external iliac lymph nodes. During such dissections the nerve should be isolated and preserved if possible. Neural deficits include groin pain and paresthesia over the ipsilateral mons, labia, and anterior thigh below the inguinal ligament (Bradshaw and Advincula 2010; Irvin et al. 2004).

2.6 Common Peroneal

Common peroneal nerve (L4-S2) courses laterally across the knee in close proximity to bone with little superficial protection. It can be injured due to poor positioning of the knee and lower leg by pressing against the hard surface of stirrups. The nerve may be pressed against the fibular head; therefore, careful positioning, avoiding pressure on the lateral knee, and use of padding may decrease the chance of injury. Neurological deficits include paresthesia over the lateral lower leg and dorsum of the foot, weakness of ankle extension, or foot dorsiflexion. The patients typically present with foot drop (Bradshaw and Advincula 2010; Craig 2013; Irvin et al. 2004).

2.7 Sciatic Nerve

Sciatic nerve (L4-S3) courses beneath the piriformis muscle and through the greater sciatic foramen as it exits the pelvis to travel down the posterior thigh to the popliteal fossa. Injury during open surgery is rare but may result in an event of a sudden hemorrhage requiring placement of sutures deep within lateral pelvis to control bleeding. The injury has also been reported with pelvic exenteration surgery. Symptoms of injury typically involve pain as well as weakness affecting most of the lower leg musculature and hamstrings while sparing hip flexion, extension, abduction, adduction, and knee extension. Sensory loss involves the lower leg. The ankle reflex is absent, while the knee reflex is normal (Craig 2013; Irvin et al. 2004).

2.8 Obturator Nerve

Obturator nerve (L2-L4) courses through psoas muscle, passes behind the common iliac arteries and laterally to the internal iliac artery and ureter,

then runs along the lateral wall of pelvis anterior to the obturator vessels to the obturator foramen, and enters the thigh through the obturator canal. In gynecologic surgery it is most frequently injured during retroperitoneal dissection for malignancies or endometriosis resection (Cardosi et al. 2002). The nerve can be exposed with gentle medial or lateral traction on the external iliac artery and vein.

If perioperative injury is diagnosed, the damage should be immediately repaired with microsurgical technique. Nerve injury can also occur during mid-urethral sling operations, particularly the transobturator tape (TOT) procedure (Aydogmus et al. 2014). Nerve injury presents postoperatively with loss of sensation over the inner thighs and motor loss in the hip adductors. Postoperative physical therapy should be initiated promptly including neuromuscular electrical stimulation, electromyographic biofeedback, exercise, and home-treatment regimen. Complete motor recovery is common after physiotherapy (Craig 2013; Irvin et al. 2004).

3 Wound Complications

Wound complications are one of the most common causes of postoperative morbidity. Wound complications (separation, hematoma, seroma, and infection) are estimated to affect 2–5 % of abdominal incisions (Sherertz et al. 1992). Poor wound healing or collections of fluid/blood under the skin may cause the incision to separate and predispose the wound to infection.

Wound complications usually present as swelling, pain, and/or drainage of fluid from the incision, most often within 3–10 days after surgery. When infected, the wound is often erythematous, indurated, and tender. Wound infections may be accompanied by fever and/or leukocytosis.

Patients presenting in the postoperative period with any of these symptoms should be carefully evaluated with a thorough history and physical exam. Most of these complications may be managed without imaging or surgical intervention.

Wound separation: Wound separation is defined as separation of the superficial layers of the wound (subcutaneous fat and skin). The underlying fascia is intact. Wound separation in the absence of a fluid collection or infection is uncommon, and if identified within 7–10 days of the initial surgery, delayed surgical re-approximation of the wound may be considered.

Seroma/hematoma: A seroma is a collection of serum under the skin, while a hematoma is a similar collection of blood. A seroma or hematoma separates the superficial layers under the skin and prevents adequate wound healing. These wound complications are commonly related to obesity, immunocompromised and inadequate hemostasis. The fluid collects under the skin and gradually leaks out the incision line. Small hematomas and seromas (<2 cm) may be managed expectantly, while most need to be opened up and drained. During drainage of the fluid collection, it is important to evaluate whether the fascia is intact (see below on wound dehiscence). After drainage of a hematoma or seroma, the wound is generally packed with clean gauze and the wound is allowed to heal by secondary intention. This gauze packing should be removed and replaced one to two times per day to promote healing and decrease the risk of infection. When there is healthy granulation tissue present and no evidence of infection, delayed surgical re-approximation of the wound may be considered.

Abscess/superficial surgical site infection: Fluid collections under the skin are prone to infection. Infection of a fluid collection is by definition an abscess. Clinical suspicion for abscess is high when the wound appears erythematous, indurated, or warm and when the patient has fevers or leukocytosis. Superficial wound infection in the absence of abscess may be treated with antibiotics alone and close follow-up. Any wound abscess must be opened up and drained. If there is suspicion for a deep surgical site infection (infection of the fascia) or fascial disruption, then the wound exploration should be conducted in the operating room (Figs. 1 and 2). The infected wound should be irrigated, debrided down to the healthy-appearing tissue, and packed open with clean gauze. Once the infection has resolved and

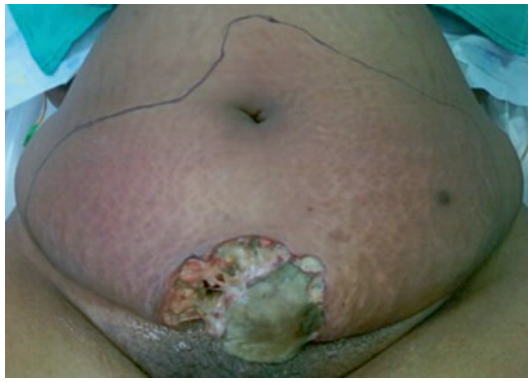

Fig. 1 Abdominal incision surgical site wound infection showing erythema, induration, exudate, and necrosis

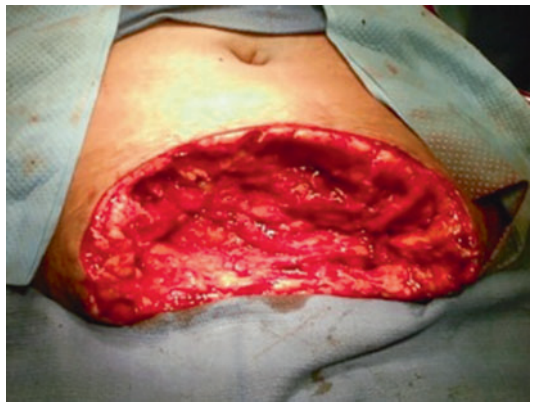

Fig. 2 Wound infection after extensive debridement showing healthy granulation tissue

granulation tissue is visible, the wound may be closed secondarily. Systemic antibiotics should be considered based on the severity/extent of the infection, presence of systemic symptoms, and medical comorbidities.

A severe form of surgical site infection is necrotizing fasciitis. Necrotizing fasciitis is usually caused by Group A *Streptococcus*, but may be polymicrobial. Necrotizing fasciitis should be considered when patients appear acutely ill, have pain out of proportion to the examination, and demonstrate significant tissue disruption or where the fluid and tissue appear gray and dusky. The skin and more superficial layers may appear relatively unaffected, while the infection involves the fascia and deep muscle layers. Necrotizing fasciitis is an acute infection with significant morbidity and mortality. It is a surgical emergency and should be aggressively treated with surgical debridement with experienced surgeons. Surgical exploration is the only way to accurately diagnose necrotizing fasciitis.

Wound (fascial) dehiscence: Wound dehiscence occurs when there is separation of the fascial layers, which provide the majority of support for the abdominal wall. Fascial dehiscence is estimated to affect 0.4–3.5 % of abdominal surgeries (van Ramshorst et al. 2010). With early fascial dehiscence, the skin may be intact. The patient may report a "popping" sensation upon sitting up or coughing, or the wound may start to leak copious amounts of serosanguinous fluid. The wound should be evaluated for fascial integrity, and any suspicion for fascial dehiscence is a surgical emergency, as the patient is at risk for evisceration.

Evisceration: Evisceration is fascial dehiscence with extrusion of abdominal contents into the incision or onto the abdomen. Evisceration is a surgical emergency, as the exposed bowel may undergo swelling and necrosis. Patients with evisceration should be covered with sterile towels and taken immediately for surgical repair.

4 Cuff Infection

Deep surgical site infections are an uncommon complication after hysterectomy. The rate of infection generally ranges from 1 % to 3 % (Mahdi et al. 2014). Deep surgical site infections after gynecologic surgery are usually polymicrobial and often represent the endogenous flora of the patient's skin or vagina (Duff and Park 1980; ACOG 2009).

Patients generally present with pain, fever, tachycardia, and tachypnea. Cuff infections are usually identified in the first few days to weeks after hysterectomy. On pelvic exam, the vaginal cuff is diffusely tender and a fluctuant mass may be palpable. Laboratory findings are consistent with systemic infection and include leukocytosis with left shift, elevated erythrocyte sedimentation rate, and an elevated C-reactive protein (Jaiyeoba 2012). Cuff tenderness and evidence of infection

are indicative of cuff cellulitis, while such evidence of infection in the setting of a complex fluid collection is suggestive of pelvic abscess.

Any patient with a suspecte pelvic abscess should undergo imaging, usually via computed tomography (CT). CT allows for delineation of the abscess, as well as evaluation of the surrounding organs, which can help rule out bowel or bladder injury as the etiology of the infection.

Postoperative cuff cellulitis may be treated empirically with antibiotics and close monitoring. Broad spectrum antibiotics covering aerobic and anaerobic bacteria are usually effective for cellulitis and for abscesses less than 2 cm (Greenstein et al. 2013). For larger abscesses, percutaneous or surgical drainage should be considered. Percutaneous drainage can be accomplished using ultrasound or CT guidance and may be approached transabdominally, transgluteally, or transvaginally.

In patients with abscesses that fail to respond to percutaneous drainage and antibiotics, surgical drainage should be considered. Surgical drainage can be accomplished via laparotomy or laparoscopy, depending on the stability of the patient. Surgical evaluation can confirm the diagnosis, obtain cultures to guide postoperative antibiotic treatment, and remove the abscess/necrotic tissue. Copious irrigation is used and a drain is usually left in situ.

5 Cuff Evisceration

Vaginal cuff evisceration is the dehiscence of the vaginal tissue with associated prolapse of small bowel through the vagina (Fig. 8). Vaginal cuff evisceration is extremely rare, and estimates range from 0.032 % to 1.2 % (Ceccaroni et al. 2011; Croak et al. 2004; Kho et al. 2009). Patients with cuff evisceration most commonly present with pelvic/abdominal pain and vaginal bleeding or watery discharge (Cronin et al. 2012). However, they may be asymptomatic. These patients typically present in the first 6 weeks after surgery, but may present up to 30 years later (Cronin et al. 2012). Some cases are precipitated by intercourse, defecation, or Valsalva (such as cough or sneeze); however, the majority of cases are spontaneous (Croak et al. 2004; Nick et al. 2011).

Asymptomatic cuff separation without evisceration may be managed expectantly and left to close by secondary intention. Once the bowel has eviscerated, surgical management is necessary. Surgical closure of the cuff may be accomplished vaginally, laparoscopically, or via laparotomy. There is not enough data to recommend one approach over another. If the bowel is compromised, then laparoscopic or open technique should be undertaken with resection of nonviable bowel. If the prolapsed bowel is viable, then the approach may be laparoscopic, open, or vaginal (Gandhi and Jha 2011). Laparoscopic and open techniques allow the surgeon to fully evaluate the bowel for any injuries. The vaginal approach has lower morbidity and allows recovery without any abdominal incisions (Cronin et al. 2012).

6 Delayed Complications Presenting in the Early Postoperative Period (Within 3 Months)

6.1 Urinary Tract Fistulae

The most common operative complication during hysterectomy or cesarean section is urinary tract injury. The exact prevalence of bladder and ureteral injury during obstetric/gynecologic surgery is unknown, though estimates range from 0.3 % to 4.3 % (Teeluckdharry et al. 2015).

The bladder is most commonly injured during (1) entry into the peritoneal cavity, (2) development of the bladder flap at the time of cesarean section or hysterectomy, or (3) closure of the vaginal cuff at the time of hysterectomy. The ureters are less commonly injured, but are most vulnerable at the time of ligation of the ovarian vessels and ligation of the uterine vessels or during transection of the vaginal cuff.

Many urinary tract injuries are recognized and repaired intraoperatively and usually heal well. Sometimes injuries may be detected in the immediate postoperative period (within 1–4 days).

Table 1 Examples of common fistulae and their nomenclature

Organ 1	Organ 2	Fistula
Bladder	Vagina	Vesico-vaginal
Bladder	Uterus	Vesico-uterine
Ureter	Vagina	Ureterovaginal
Ureter	Uterus	Uretero-uterine
Rectum	Vagina	Rectovaginal
Small bowel	Vagina	Enterovaginal
Small bowel	Skin	Entero-cutaneous

These usually present as fever, unilateral or bilateral flank pain, and/or the inability to urinate. Damage to the ureter or bladder may result in leakage of urine into the peritoneal cavity, which then is reabsorbed, causing an elevation in creatinine. This collection of fluid may be detected on ultrasound or computed tomography (CT) scan, and any postoperative patient with these symptoms should be evaluated with a high index of suspicion for ureteral or bladder injury. The typical workup includes: careful physical examination, measurement of serum creatinine, pelvic/abdominal ultrasound, or CT scan. If a collection of urine (urinoma) is found, then prompt consultation by a urologic surgeon is needed to determine if immediate surgical repair may be indicated to reduce further postoperative complications, such as genitourinary fistula (Tables 1 and 2).

6.1.1 Postoperative Recognition

It is impossible to know how many unrecognized injuries heal spontaneously. However, it is clear that some unrecognized injuries may result in serious sequelae. The most common sequela of a bladder or ureteral injury is an abnormal communication between two organs called a fistula. The incidence of genitourinary fistulae after gynecologic surgery is estimated to range between 0.13 % and 2 % (Meeks and Roth 2011; Adelman et al. 2014).

Fistulae classically present within 7–30 days after surgery. Patients usually complain of painless leakage of urine or fluid from the vagina. Anyone with leakage of fluid from the vagina should undergo a careful physical exam to determine the source and consistency of the leakage. The fluid may be examined by wet mount and culture to evaluate for infection and by urinalysis to confirm a urinary source. Often it may be difficult to identify the source of the leakage of the fluid, and the bladder may be evaluated by one of several techniques:

1. Filling the bladder with blue fluid (usually normal saline with a few drops of methylene blue) and looking for leakage of blue fluid in the vagina.
2. Cystoscopy: A cystoscope is inserted through the urethra to directly visualize the inside surface of the bladder. A fistula may be directly identified using this technique.
3. Cystogram: Radio-opaque dye is instilled into the bladder and leakage is identified by X-ray. Care must be taken to exclude urinary incontinence (leakage from the urethra) that may mimic a fistula on X-ray (Fig. 3).
4. CT Urogram: Computerized tomography is used to evaluate the integrity of the bladder and upper urinary tract.

It is important to remember that multiple injuries may coexist. Injury to the bladder may signify additional injury to the distal ureter, and ureterovaginal fistula must be ruled out, even if a vesico-vaginal fistula has been diagnosed. The ureter is usually evaluated using a CT urogram or an intravenous pyelogram.

When identified, the first treatment for a genitourinary fistula is continuous bladder drainage while the injury heals. With continuous drainage via transurethral catheter, small fistulas may heal without surgical intervention. Continuous catheterization is usually recommended for 6 weeks to 3 months after the initial injury. Once the inflammatory stage of wound healing is completed, if the connection is still present, then surgery is necessary to treat the fistula.

Surgical repair may be attempted vaginally, laparoscopically, or via open abdominal surgery. Surgical approach depends on surgeon preference, health of the surrounding tissue, the size and location of the fistula, and whether it has been repaired before. Generally the first repair of most fistulas is attempted vaginally, especially for small fistulas just above the trigone of the bladder.

Table 2 Nerves commonly injured in gynecologic surgery

Nerve	Nerve roots	Motor function	Sensory function	Presenting symptom	Mode of injury
Ilioinguinal, iliohypogastric	T12-L1	None	Mons pubis, labia, and inner thigh	Pain at the incision site that radiates to the groin. Paresthesia over mons pubis, labia, and inner thigh	Direct surgical injury or nerve incorporation during fascial closure
Genitofemoral	L1-L2	None	Mons, labia, and anterior thigh below the inguinal ligament	Groin pain and paresthesia over the ipsilateral mons, labia, and anterior thigh below the inguinal ligament	Compression from retractors. Retroperitoneal dissection
Femoral	L2-L4	Hip flexion, adduction, knee extension	Anterior thigh, medial leg	Weakness of hip flexion, knee extension. Unstable knee, unable to climb stairs, absent patellar reflex	Compression from retractors. Improper positioning in lithotomy
Lateral femoral cutaneous	L2-L3	None	Anterior lateral thigh	Numbness, paresthesia, and pain over the anterior lateral thigh from the inguinal ligament to the knee	Compression from retractors. Improper positioning in lithotomy
Obturator	L2-L4	Thigh adduction	Inner thigh	Weakness of thigh adduction. Paresthesias/ numbness over inner thigh	Retroperitoneal dissection. Transobturator mid-urethral sling
Sciatic	L4-S3	Lower leg musculature and hamstrings	Lower leg	Weakness of most of the lower leg musculature and hamstrings, spared hip flexion, extension, abduction, adduction, and knee extension. Paresthesia/ numbness of the lower leg. Absent ankle reflex, but normal knee reflex	Placement of sutures deep within lateral pelvis to control bleeding. Pelvic exenteration surgery
Common peroneal	L4-S2	Ankle extension and foot dorsiflexion	Lateral lower leg and dorsum of the foot	Foot drop (poor foot dorsiflexion). Paresthesia over lateral lower leg and dorsum of foot	Poor positioning of the knee and lower leg against the hard surface of stirrups

Abdominal/laparoscopic procedures are reserved for complicated repairs, repeat procedures, and patients who have been irradiated or those with extremely large injuries or ureteral involvement.

7 Rectovaginal and Enterovaginal Fistulae

Injury to the large or small intestines is one of the most dreaded intraoperative complications from ob/gyn surgery. Acute injury, when repaired intraoperatively, generally has little consequence. However, unrecognized bowel injury is one of the most significant causes of postoperative morbidity and mortality. Acute injury may be identified within the first few days of surgery and is discussed elsewhere. Chronic injury may result in a fistulous tract.

Any leakage of fecal contents from the vagina should be evaluated promptly. Rectal injuries are common after vaginal deliveries, particularly after instrumented deliveries using vacuum or forceps. These injuries are usually repaired at the time of delivery, but may break down or be inadequately repaired.

Leakage of gas or liquid stool from the vagina is the presenting complaint of women with a

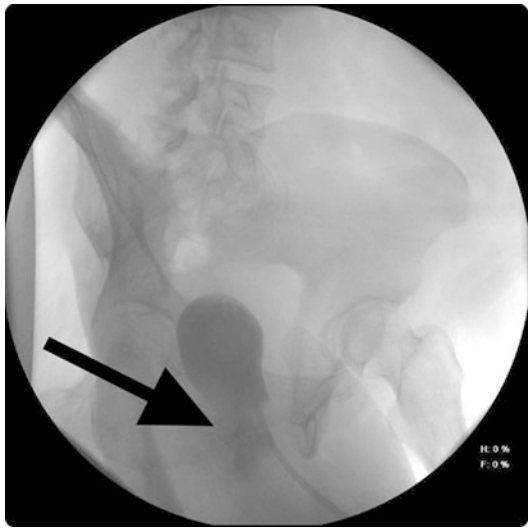

Fig. 3 Cystogram showing large defect in the bladder with extravasation of dye into the vagina (Originally published in: Wild et al. 2012; with kind permission of Elsevier. All rights reserved)

rectovaginal fistula. Leakage of solid stool is usually indicative of a large fistula or a defect in the anal sphincter. These distal connections can often be found on careful physical exam with a finger in the rectum. Any defect can be gently probed with a cotton-tipped swab or a small instrument. The connection can usually be identified in this manner (Fig. 4).

Similar to urinary tract fistulae, rectovaginal fistulae are generally allowed to heal until all inflammatory and granulation tissue is resolved. The tract is then surgically excised and the intervening tissue repaired in layers. Postoperatively, the patient is encouraged to have bulky, soft bowel movements for 3 months, through aggressive dietary and bowel management.

Connections higher up in the rectum or involving the large bowel may be identified on colonoscopy or using X-ray in conjunction with a radiopaque enema. Connections involving the small intestines are difficult to diagnose and may require computed tomography. Fistulas involving the small or large bowel should be managed in cooperation with a colorectal surgeon.

8 Thromboembolism

Venous thromboembolism is the leading cause of postoperative mortality. Deep vein thrombosis (DVT) is usually occult and may resolve without complication, and death from DVT-associated pulmonary embolism (PE) is responsible for up to 300,000 deaths annually in the United States alone (Tapson 2008).

Venous thrombosis is caused by activation of the clotting mechanism within the venous circulation. These blood clots may become dislodged and migrate to the right heart and pulmonary artery, where they may result in occlusion and cardiac strain.

The postoperative period is a time of increased risk for venous thromboembolism due to: (1) venous stasis due to paralysis during surgery, (2) perioperative release of coagulation factors, and (3) the relative immobility of the postoperative period. Many studies have shown that perioperative treatment with sequential compression devices, chemoprophylaxis, and early/aggressive ambulation are all effective at decreasing the risk of perioperative thromboembolism.

The most common presentation of DVT is (often unilateral) edema, leg pain, leg tenderness, and warmth or erythema of the skin over the thrombosis. Pulmonary embolism may manifest as acute shortness of breath or chest pain and may be the presenting symptom of DVT.

Physical exam findings are nonspecific. Patients may demonstrate calf pain upon dorsiflexion of the foot (Homans' sign). They may demonstrate a palpable cordlike section of vein along the posterior of the calf. This "cord" may or may not be tender to palpation.

Further evaluation is necessary when considering a diagnosis of DVT. The American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) recommend a complete workup including the following (Qaseem et al. 2007; Snow et al. 2007):

Clinical parameter to predict DVT (Wells et al. 1997)	Score
Active cancer	+1
	+1

(*continued*)

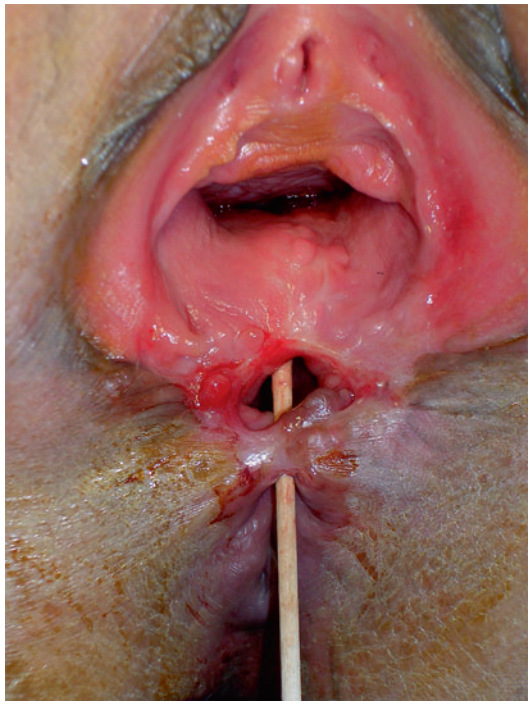

Fig. 4 Rectovaginal fistula

Clinical parameter to predict DVT (Wells et al. 1997)	Score
Paralysis or recent plaster immobilization of lower extremities	
Recently bedridden for more than 3 days or major surgery within 12 weeks	+1
Local tenderness in the distribution of the deep venous system	+1
Entire leg swollen	+1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg	+1
Collateral superficial veins (non-varicose)	+1
Alternative diagnosis at least as likely as DVT	−2

Pretest assessment of clinical factors uses validated criteria, such as the Wells criteria. The Wells criteria to predict DVT include nine different clinical factors, which are scored as a clinical probability. A score of $<=0$ is low, 1–2 is intermediate, and $>=3$ is high.

In patients with a low pretest probability based on clinical criteria, a high-sensitivity D-dimer assay may be used to rule out DVT. If the D-dimer assay is positive, or if the patient is older/has significant comorbidities, then further testing is indicated.

Doppler ultrasound testing of the venous system is recommended for anyone with intermediate or high scoring of clinical criteria. Doppler ultrasound of the calf may be negative; therefore, if suspicious of DVT confined to the calf, repeat ultrasound testing or contrast venography may be indicated.

If suspicious for pulmonary embolism, pretest assessment of clinical factors should similarly be performed. Wells criteria to predict PE include six different clinical factors, and similar to the Wells score for DVT, the Wells score for PE is scored as low, intermediate, or high probability; a score of 0–1 is low risk, 2–6 is intermediate risk, and $>=7$ is high risk.

Clinical parameter to predict PE (van Belle et al. 2006)	Score
Previous PE or DVT	+1.5
Heart rate >100 beats per minute	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of deep venous thrombosis	+3
Alternative diagnosis less likely than pulmonary embolism	+3
Hemoptysis	+1
Cancer	+1

If the clinical suspicion for DVT or PE is high, it is reasonable to begin treatment while the workup is confirming the diagnosis. The risks of untreated DVT or PE are high and may outweigh the risks of a brief treatment of anticoagulation, even if such treatment is ultimately unnecessary.

Once diagnosed, the mainstay of treatment for DVT or PE is anticoagulation. Low-molecular-weight heparin (LMWH) should be used for initial inpatient treatment of DVT. LMWH is superior to unfractionated heparin for the treatment of DVT for ease of dosing and maintenance, as well as an overall reduction in mortality and major bleeding. Treatment is generally administered for 3–6 months for DVT due to transient risk factors such as surgery. Outpatient treatment is reasonable and may consist of daily injections with LMWH or transition to an oral treatment, such as a vitamin K antagonist. Compression stockings should be used to prevent post-thrombotic syndrome, a chronic syndrome of leg pain, swelling,

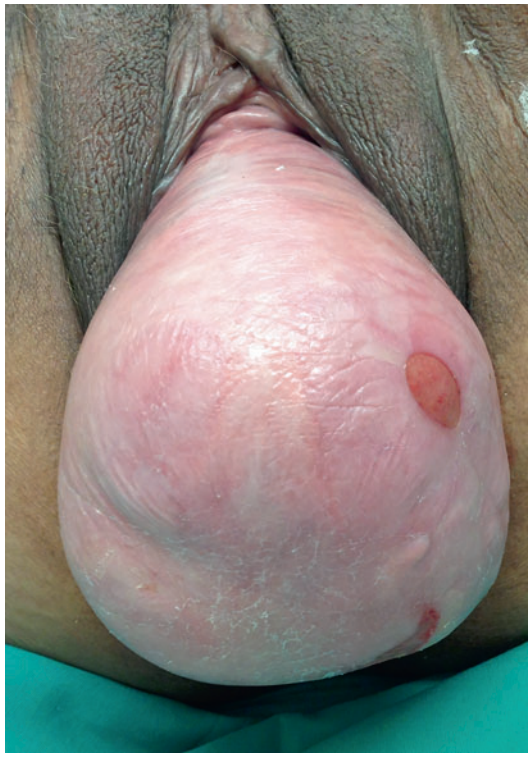

Fig. 5 Pelvic organ prolapse after hysterectomy

and ulceration that occurs in up to half of patients with DVT. The stockings should be worn staring within 1 month of DVT diagnosis and continued for at least a year (Vazquez and Kahn 2010).

9 Delayed Complications Presenting in the Late Postoperative Period (Months to Years)

9.1 Pelvic Organ Prolapse

Pelvic organ prolapse is the descent of any of the pelvic organs. Hysterectomy is a known risk factor for the development of pelvic organ prolapse. A large study of community dwelling women found that women with prolapse were 1.68× more likely to have undergone a prior hysterectomy (Lawrence et al. 2008). The incidence of prolapse after hysterectomy is higher for women who had a hysterectomy for prolapse (1.6–11.6 %) compared to women who had a hysterectomy for other indications (0.3–1.8 %) (Mant et al. 1997; Marchionni et al. 1999).

The main symptom of pelvic organ prolapse is the sensation of pressure or bulge in the vagina (Fig. 5). Severe complications of prolapse are rare. Prolapse diagnosis is usually based on physical exam, though several formal staging systems exist. Asymptomatic or minimally symptomatic prolapse may not require any intervention. Patients with significant bother may elect to use a plastic device (pessary) to hold their prolapsed organs in place, or they may elect for surgery. There are a variety of surgical procedures for prolapse, depending on the patient's health, preferences, degree, and location of prolapse.

9.1.1 Cuff Complications

Granulation Tissue

The most common abnormal postoperative finding at the vaginal cuff is granulation tissue. Granulation tissue is an over-proliferation of healing tissue that may be found on any wound. Granulation tissue is usually described as beefy red and friable (see Fig. 6).

Most cases of vaginal granulation tissue are asymptomatic, but may also cause vaginal bleeding, particularly after intercourse. Granulation tissue at the cuff is benign and may be treated with topical cautery using (Saropola and Ingsirorat 1998) sticks or may be excised. Excision may be preferred when the tissue is large and symptomatic or if the diagnosis is in question. Other conditions may occasionally be mistaken for granulation tissue, including malignancy or fallopian tube prolapse (Song et al. 2005).

Fallopian Tube Prolapse

Fallopian tube prolapse is a rare complication of hysterectomy, whereby the fallopian tube is either incorporated into the vaginal cuff or prolapses through an open cuff. This complication usually presents with severe low abdominal pain or a pulling sensation and tenderness to palpation of the cuff. The tube may be visible at the apex of the vagina, and biopsy or excisional biopsy can confirm the diagnosis (Figs. 7 and 8).

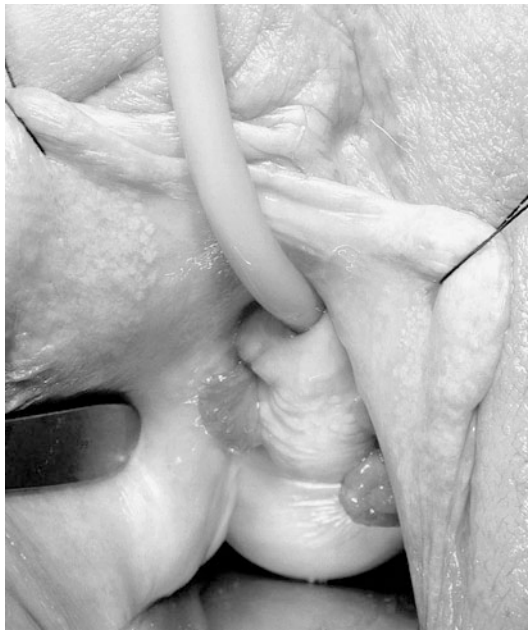

Fig. 6 Granulation tissue at cuff (Originally published in: Stember et al. 2003; with kind permission of Springer Science + Business Media. All rights reserved)

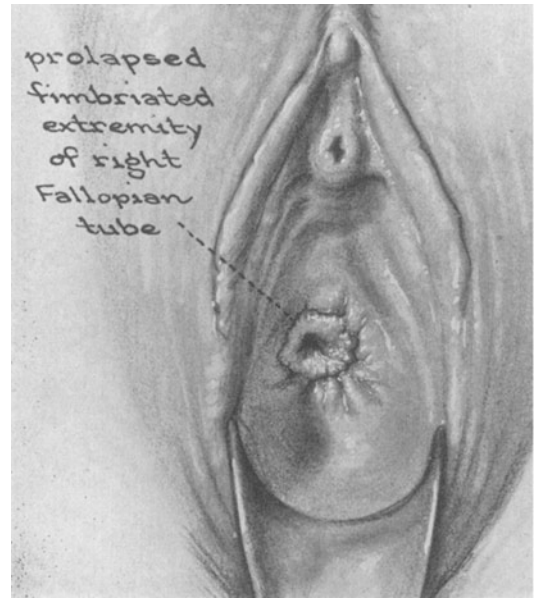

Fig. 7 Fallopian tube prolapse (Originally published in: Bower et al. 1940; with kind permission of Elsevier. All rights reserved)

If the diagnosis is confirmed, revision of the cuff is usually necessary to relieve symptoms. This revision may be performed vaginally, and the cuff is opened up, the damaged tube is often excised, and the remaining cuff is closed. Laparoscopic/open approach may also allow confirmation of diagnosis and evaluation for additional etiologies of the pain.

10 Conclusion

All surgical procedures have the risks of postoperative complications. These complications may be immediate or delayed. Delayed postoperative complications can have serious effects for patients, and prompt diagnosis and management is critical. This chapter discusses a variety of complications that can be managed clinically or operatively. A thorough understanding of the mechanism of neurologic injury allows for insight into prevention and recognition, which can reduce the effect on the patient. Wound complications can generally be managed conservatively, and only the most severe infections or fascial dehiscences need surgical management. Fistulae are among the most dreaded complications by surgeons, as they generally represent unrecognized surgical injury; however, with prompt recognition and surgical treatment, most fistulae can be

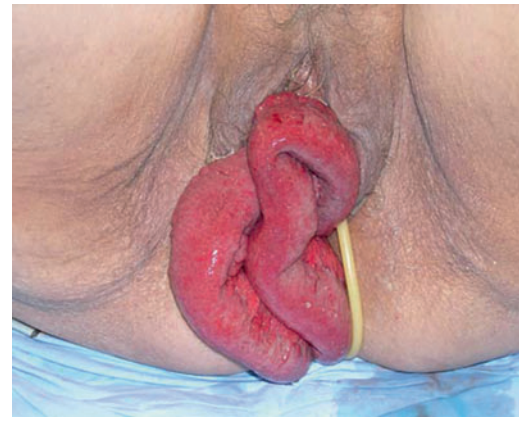

Fig. 8 Vaginal evisceration of small bowel through vaginal cuff (Originally published in: Partsinevelos et al. 2008; with kind permission of Springer Science + Business Media. All rights reserved)

completely cured. Thromboembolism is probably the most dangerous of the postoperative complications, though studies have shown improvement of morbidity and mortality with aggressive prevention and early diagnosis. Finally, pelvic organ prolapse and cuff complications are varied and require clinical insight into diagnosis and management. There is no such thing as a surgeon with no complications, but with enough understanding, preparation, and care, a surgeon can minimize their complications and mitigate the impact upon their patients.

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Breast Cancer Screening

Heather R Macdonald

Contents

Abstract

It is expected in 2016 246,660 women in the United States will be newly diagnosed with breast cancer and 40,450 women will die of the disease. The purpose of breast cancer screening is to identify preclinical disease in asymptomatic women as breast cancer survival is improved with early detection. Digital mammography remains the mainstay of breast cancer screening. Tomosynthesis (3-D mammogram) has improved sensitivity with fewer false-positive studies, especially in women with dense breasts. Concerns have been raised about harms of false positives (repeat imaging and/or biopsies for benign findings), overdiagnosis of clinically insignificant breast cancers, and overtreatment. Thus, breast cancer screening recommendations range from initiation of screening at 40 years and performed annually to initiation at 50 years and performed biannually.

All guidelines recommend cancer risk assessment with a physician and development of an individualized screening program.

Women with the strongest risk factor for breast cancer, including personal history of cancer or atypical breast biopsy or family history of breast cancer, should undergo annual screening mammography. Women known to carry a

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familial breast cancer gene or at a lifetime risk of breast cancer greater than 20% should undergo annual breast MRI in addition to annual mammogram. Screening should conclude when a woman's life expectancy is less than 5 years.

Keywords
Breast cancer risk factors • Familial breast cancer syndromes • Breast cancer risk assessment • Mammography • Breast MRI • Tomosynthesis • BIRADS score

1 Introduction

It is expected in 2016 246,660 women in the United States will be newly diagnosed with breast cancer and 40,450 women will die of the disease (American Cancer Society 2016). One in 12 women will develop breast cancer in their lifetime, a statistic that has not decreased in recent years. The purpose of breast cancer screening is to identify preclinical disease in asymptomatic women as breast cancer survival is improved with early detection (Nelson et al. 2009). Implementation of screening mammography (regular mammograms performed in asymptomatic women with normal breast exams) has been associated with improved survival from breast cancer of 23–40% (Lauby-Secretan et al. 2015). Breast cancer mortality has been dropping by 1.9% per year, likely due to a combination of improved early detection (screening) and improved treatment (Ryerson et al. 2016). However, concerns have been raised about harms of false positives (repeat imaging and or biopsies for benign findings), overdiagnosis of clinically insignificant breast cancers, and overtreatment. Thus, breast cancer screening recommendations are in flux, and the optimal age of initiation and screening interval is controversial for low-risk women. Major medical associations have released conflicting screening recommendations leading to confusion and frustration among physicians and patients. As research has demonstrated a better understanding of how breast cancer risk changes over a woman's lifetime, screening recommendations are moving to an individualized risk-based approach. This chapter will summarize the range of recommendations for breast cancer screening in low-risk women and briefly summarize the data behind them. Risk factors for breast cancer will be reviewed as well as screening recommendations for women at risk for breast cancer.

2 Who Is at Increased Risk for Breast Cancer?

Risk factors for breast cancer are listed in Table 1 with their relative risks. As demonstrated below factors associated with the highest risk of breast cancer are female gender, older age, history of previous breast cancer, family history of breast cancer in a first-degree relative, and history of atypical breast biopsy. Patients with both a family history of breast cancer in a first-degree relative and a personal history of an atypical breast biopsy are at highest risk, with relative risk approaching those of *BRCA* mutation carriers (Dupont and Page 1985).

A strong family history of breast or related cancers is a red flag for an inherited familial breast cancer syndrome. Each patient should be assessed for familial cancer syndromes by eliciting a three-generation family history that includes ethnicity, any cancers in the family, who was diagnosed with cancer and their relationship to the patient, how the cancer was diagnosed and treated, if the afflicted family member survived or died, and if any genetic testing was performed. If there is a pattern of cancers running through the family or a clustering of rare cancers occurring in related relatives, consideration should be given to a genetic counseling referral. Table 2 lists the American College of Obstetricians and Gynecologists recommendations for genetic testing and counseling. Table 3 includes characteristics of the most common familial breast cancer syndromes.

Personalized cancer risk assessment is an important tool to guide physicians and patients in quantifying breast cancer risk and designing an appropriate screening regimen. Counseling should focus on lifestyle changes targeting high-

Table 1 Risk factors for breast cancer

Risk factor	Type	Relative risk
Highest risk		
Female gender	Reproductive	**>4**
Increasing age	Reproductive	
Inherited gene mutation (i.e., *BRCA*)	Familial	
>2 young first-degree relatives with breast cancer	Familial	
Personal history of breast cancer	Personal medical history	
History of atypical breast biopsy	Personal medical history	
Moderate risk		
One first-degree relative with breast cancer	Familial	**2.1–4**
History of chest wall radiation <30	Personal medical history	
Slightly increased risk		
First term birth >30 years	Reproductive	**1.1–2**
Menarche <12 years	Reproductive	
Menopause >55	Reproductive	
Nulliparity	Reproductive	
No history of breast feeding	Reproductive	
Use of combination hormone replacement therapy	Personal medical history	
Postmenopausal weight gain	Lifestyle	
Alcohol consumption	Lifestyle	
Smoking	Lifestyle	
Physical inactivity	Lifestyle	

Table 2 ACOG recommendations for genetic counseling referral

Cancer diagnosed at young age (i.e., breast cancer younger than 50)
Several different cancer diagnoses in the same individual (i.e., breast and ovarian or colon and endometrial)
Close blood relatives with the same type of cancer (i.e., mother-daughter pairs)
Unusual cancer presentation (i.e., male relative with breast cancer)
Ashkenazi Jewish ancestry
Occurrence of adult cancer known to be associated with familial cancer syndromes:
Triple negative breast cancer (ER/PR/her 2 neu negative suggestive of BRCA 1 mutation)
Epithelial or serous ovarian cancer (suggestive of a BRCA mutation)
Colorectal or endometrial cancer with DNA mismatch repair deficiency (suggestive of Lynch syndrome)

Table 3 Familial breast cancer syndromes

Syndrome	Gene mutation	Lifetime breast cancer risk	Associated cancers
Hereditary breast and ovarian cancer syndrome	*BRCA 1* and *2*	80% (*BRCA 1*)	Ovarian
		60% (*BRCA 2*)	Prostate
			Pancreatic
			Melanoma
Li-Fraumeni	*p53*	90% (all cancer types)	Bone and soft tissue sarcoma
			Brain
			Adrenocorticoid
			Colon
			Leukemia
Cowden	*pTEN*	30–50%	Endometrial
			Nonmedullary thyroid
Hereditary diffuse gastric cancer	*CDH1*	40–50%	Lobular breast cancer
			Diffuse gastric cancer

risk behaviors (see lifestyle factors above) and estimating risk from intrinsic risk factors like family history, past medical history, and atypical cells on biopsy. Clinicians should be aware of the various familial breast cancer syndromes and refer patients with suspicious family history for genetic counseling and possible genetic testing. Table 3 describes the more common hereditary cancer syndromes and relative risks of breast cancer. For further discussion of ovarian cancer, please see the chapter entitled "Diagnosis and Management of Epithelial Ovarian Cancer."

The US Preventive Services Task Force recommended in 2009 each patient consult their physician regarding their personal risk of breast cancer and designs an individualized screening program (Nelson et al. 2009). Several online calculators have been designed and made publicly available to assist in breast cancer risk assessment, including the Gail model, IBIS, and BRCAPro. They incorporate varying details of family history, population-based risk factors like menstrual history and age at first birth, as well as personal history of breast atypia. For the highest risk patients, if lifetime breast cancer risk exceeds 20%, annual screening breast MRI is recommended (National Comprehensive Cancer Network 2016). Please see "Breast MRI" section for further explanation.

3 Breast Screening Techniques and Technologies

Breast screening modalities include breast exam, self-administered (self breast exam or SBE) or by a clinician (clinical breast exam or CBE), mammography which can include full field, digital, or tomosynthesis (three dimensional), breast ultrasound, or breast MRI. Table 4 lists the sensitivities and specificities of each. The remainder of the chapter will discuss the relative advantages and drawbacks to each.

Table 4 Sensitivity of common breast cancer screening modalities

Modality	Sensitivity	Specificity
Self breast exam	2–4%	Finds more benign than malignant disease
Clinical breast exam	40–69%	88–99%
Mammography	77–95%	94–97%
Tomosynthesis	90%	79%
Breast MRI	71–100%	81–97%

3.1 Breast Exam

Breast exam is the most commonly utilized breast screening tool but is falling out of favor due to low sensitivity and specificity. Self breast exam has been demonstrated to increase patient anxiety without improving cancer detection and is no longer routinely recommended. Breast self-awareness can be taught at a routine health maintenance visit. It entails being aware of the normal texture of one's breast tissue, as well as knowledge of any benign masses or cysts that may be present, so a patient can seek medical attention if changes occur. Breast self-awareness should also involve education of menstrual patients regarding the expected fluctuations in breast tissue associated with phases of the menstrual cycle.

3.2 Clinical Breast Exam

Clinical breast exam is perhaps the most commonly utilized breast cancer screening tool as it is commonly included in well woman annual health screening. However, because of its low sensitivity, annual CBE is no longer recommended outside high-risk patient populations.

3.3 Mammography

Screening mammography is the mainstay of breast cancer screening. The identification of breast cancer before it becomes clinically apparent leads to improved survival, as demonstrated in several randomized control trials in the United States and Europe starting in the 1970s. Screen-detected cancers were diagnosed at earlier stage and led to lower cancer-related mortality (Tabar

Table 5 Summary of breast cancer screening recommendations

Society	Age	Recommended screening for average-risk women
American Cancer Society	40–44	Optional annual screening mammogram
	45–55	Annual screening mammogram
	>55	Screening mammogram every 2 years; screen until life expectancy is >10 years
US Preventive Services Task Force	40–49	Screening optional at patient's discretion
	50–74	Screening mammogram every 2 years
	>75	No recommendations due to lack of evidence
American College of Obstetricians and Gynecologists	>40	Annual screening mammogram
American College of Radiology	>40	Annual screening mammogram
National Cancer Institute	>40	Annual screening mammogram
National Comprehensive Cancer Network	>40	Annual screening mammogram

et al. 1985, 2000; Andersson et al. 1988). This was confirmed in subsequent meta-analyses (Oeffinger et al. 2015). Recently, controversy has arisen over screening guidelines for average-risk women, specifically at what age to initiate regular screening and at what frequency (Nelson et al. 2009). Concerns were raised by the US Preventive Services Task Force in 2009 regarding potential harms of overscreening including false-positive studies requiring additional imaging and/or biopsy and overdiagnosis leading to over-treatment and additional costs. The American Cancer Society stratified their screening recommendations by age-adjusted risk. The American College of Radiology and American College of Obstetricians and Gynecologists have continued to recommend annual screening due to benefits of early detection. Table 5 summarizes recommendations from several major medical societies regarding screening mammogram for average-risk women. Women with a high risk factor like breast atypia should undergo screening mammogram annually. Women with a family history of breast cancer should undergo screening mammography annually starting 5–10 years younger than the youngest affected family member or at age 30. For the women with extensive family history, MRI should be considered in addition to annual mammography. (Please see "MRI" section.)

The variation among recommendations has caused confusion among patients and providers and concern regarding insurance coverage of breast cancer screening in women under 50. A careful reading of all published guidelines demonstrates an emphasis by each of personalized screening based on the patient's risk factors and concern regarding cancer detection. Guidelines agree that average-risk women should have the option to start mammographic screening at 40 should they desire screening for early cancer detection and understand the risks of false-positive studies.

3.4 Tomosynthesis

A major advance in mammographic screening has been three-dimensional digital breast tomosynthesis (DBT). Tomosynthesis takes a series of images that allows the mammographer to review images in thin reconstructed slices, allowing the viewer to scroll up and down or side to side through breast tissues. Radiation exposure is comparable to standard mammography (Gur et al. 2009). The technology is better able to discern overlapping normal tissues and underlying lesions (Lei et al. 2014). Tomosynthesis was found in a recent meta-analysis of breast imaging techniques to have a higher sensitivity and specificity (90% and 79%, respectively) than digital and plain field mammography. DBT was found to have reduced recall rate and improved detection of breast lesions, resulting in fewer false positives and false negatives. It has been found to be most effective with increased invasive cancer detection

rate when used in conjunction with full-field digital mammography but requires two radiation exposures of the patient (Hodgson et al. 2016). Patients with dense breasts may particularly benefit from tomosynthesis as a screening technique. Dense breasts impede cancer detection on screening mammography as suspicious lesions can be obscured by overlapping dense tissues. By allowing mammographers to scroll through breast tissue in 1 mm slices, tomosynthesis has been shown to increase cancer detection and reduce false-positive studies in women with dense breasts (Houssami and Turner 2016).

3.5 Breast Ultrasound

Breast ultrasound has been investigated as a breast screening tool due to its ease of use, minimal patient discomfort, and lack of radiation exposure. It has been demonstrated to minimally improve cancer detection but at the cost of increased false-positive studies prompting further investigations to identify benign disease (Berg et al. 2008). Thus, it remains a diagnostic tool, useful for clarifying physical exam, mammography, or MRI findings and assessing axillary lymph nodes.

3.6 Breast MRI

Breast MRI affords the greatest sensitivity for breast cancer detection. Utilizing intravenous contrast, breast MRI demonstrates blood flow through the breast in addition to detailed soft tissue imaging, highlighting cancers by both their appearance and their preferential perfusion. Limitations include risks of false positives, limited resources (breast MRI requires a dedicated breast coil and software), placement of intravenous access, and contrast administration. Contrast allergies are rare but can occur, and IV contrast is contraindicated in patients with underlying renal disease. Additionally claustrophobic patients may find MRI challenging.

Generally, when lifetime risk of breast cancer exceeds 20%, consideration should be given to add annual breast MRI to annual mammogram. For women with a family history of breast cancer, screening with annual mammography is recommended to begin 10 years younger than the youngest affected family member, although not before 30. Patients who carry a *BRCA* mutation screening with annual breast MRI are recommended to start at 25 years with the addition of annual breast mammogram at 30. Women who have a history of an atypical breast biopsy are recommended to undergo annual screening mammography starting at 40 or at the time of identification of the lesion.

4 Characterization of Image-Detected Breast Lesions

Lesions identified on mammography that raise the concern of breast cancer include calcifications, masses, architectural distortion, and asymmetry. To reduce confusion regarding mammographic findings, the American College of Radiology has devised a scoring system that reflects levels of concern for occult malignancy. Table 6 summarizes the BIRADS scoring system and the associated risk of cancer.

Table 6 Summary of BIRADS scoring system of radiographically detected breast lesions

BIRADS score	Description	Associated risk of breast cancer
0	Incomplete	Needs additional testing
1	Negative	No or minimal risk
2	Benign	No or minimal risk
3	Probably benign	0–2%
4	Suspicious	2–95%
4A	Low suspicion	2–10%
4B	Moderate suspicion	10–50%
4C	High suspicion	50–90%
5	Highly suspicious	95% or greater
6	Tissue-confirmed cancer	Biopsy-proven cancer

Modified from Sickles et al. (2013. http://www.acr.org/Quality-Safety/Resources/BIRADS/About-BIRADS/How-to-Cite-BIRADS)

Table 7 Summary of breast screening protocol

Population	Modality	Age at initiation	Frequency
All women	Clinical breast exam and breast cancer education	20 years	Annual
Average-risk women	Mammography	40–50 years	1–2 years
Increased-risk women	Mammography	40 years	Annual
Women with a family history of breast cancer	Mammography	10 years younger than the youngest affected family member or 25 years	Annual
Familial breast cancer syndrome or known gene mutation carriers	Mammography and breast MRI	25 years (MRI)	Annual
		30 years (mammography)	

Low-risk lesions (BIRADS 3) should be reevaluated with short-term repeat imaging, usually in 6 months. Lesions that confer a suspicion of cancer (BIRADS 4 or 5) warrant a biopsy. Image-guided needle biopsy is preferable over open surgical biopsy to allow for most complete evaluation while minimizing risk to the patient (Silverstein et al. 2005). Needle biopsy has not been shown to cause cancer metastasis and avoids the risks of surgery for patients with benign lesions. Discordant biopsies (benign results in a highly suspicious lesion) should be further evaluated by repeat needle biopsy or surgical excision to avoid missing an underlying breast cancer.

5 When to Conclude Breast Cancer Screening

Breast cancer risk continues to rise through the eighth decade of life and remain elevated until the end of life (American Cancer Society 2016). More than one-third of cases are diagnosed after age 65 years (cite 2007 lancet oncology). There are no randomized control studies demonstrating a survival benefit from breast cancer screening over age 70 (Nelson et al. 2009). When to stop screening is confusing. The US Preventive Services Task Force declined to issue a recommendation regarding breast cancer screening due to lack of evidence. Because breast cancer risk remains elevated in later decades of life and women are living longer and with better health, most experts including the American Cancer Society recommend an individualized decision between the patient and physician regarding ongoing breast cancer screening.

If the patient is in good health and has life expectancy of more than 5–10 years, then continuing screening mammography is reasonable.

6 Conclusion

Despite recent confusion regarding breast cancer screening, early detection of breast cancer remains an important method to reduce breast cancer mortality and improve survival. Individualized breast cancer risk assessment allows physicians to educate patients about modifiable risk factors and design a personalized screening regimen. Screening guidelines are conflicting for average-risk women only; all guidelines agree that at-risk women should undergo annual screening mammography. By encouraging a dialogue between patients and providers regarding breast cancer risk, benefits of early detection and intervention, and harms of false-positive studies, providers can increase breast cancer awareness. Table 7 summarizes a reasonable approach to breast cancer screening.

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Benign Diseases of the Vulva

Sigita Cahoon

Contents

Abstract

Many benign diseases can affect the vulva. These varied conditions can present similarly, often with pain, burning, pruritus, vaginal discharge, and dyspareunia. Physical exam findings can be nonspecific, with erythema, excoriations, and lichenification. Contact dermatitis is a frequent cause of vulvar pruritus and pain, and nearly all topical vaginal products can cause irritation. Removal of common irritants usually results in disease resolution. Lichen simplex chronicus is a condition characterized by severe pruritus leading to a persistent itch-scratch cycle. Lichen planus is a chronic, immune-mediated dermatosis presenting with pruritic papules on the vulvar skin and white lacy striae on mucosal surfaces. Lichen sclerosus is an immune-mediated disorder that results in waxy white "cigarette paper" changes to vulvar skin and can also affect the perianal region resulting in a classic "figure of eight" appearance. Patients with lichen sclerosus should be followed closely due to an increased risk of vulvar squamous cell carcinoma. Psoriasis is a dermatologic condition which can manifest as painful and pruritic vulvar erythema. Topical corticosteroids are the first-line therapy for lichen simplex chronicus, lichen planus, lichen sclerosus, and vulvar psoriasis. Vulvar intraepithelial neoplasia (VIN) is a premalignant condition which can present variably with raised or flat lesions, ranging in color from white to red or

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black. It can be associated with carcinogenic human papillomavirus (HPV) infections as well as with vulvar dermatoses. All cases should be treated, and options range from excision, to laser ablation, to topical medical therapy with Imiquimod. Patients remain at risk for recurrence and require continued surveillance.

Keywords
Vulva • Dermatoses • Contact dermatitis • Lichen simplex chronicus • Lichen planus • Lichen sclerosus • Psoriasis • Vulvar intraepithelial neoplasia • VIN

1 Introduction

This chapter focuses on the diagnosis and management of common benign vulvar diseases. Benign vulvar disease encompasses numerous disorders, including infections, autoimmune diseases, topical irritation, dermatoses, neoplasms, cysts, and masses. Many of these varied diseases can present quite similarly. Patients often complain of vulvar irritation, burning, pain, pruritus, dysuria, dyspareunia, and vaginal discharge. On exam many vulvar conditions appear similar, with erythema, edema, signs of excoriations leading to ulcerations, and lichenification in cases of chronic scratching. This review will focus primarily on dermatoses commonly affecting the vulvovaginal region, including contact dermatitis, lichen simplex chronicus, lichen planus, and lichen sclerosus, as well as psoriasis and vulvar intraepithelial neoplasia.

Diagnoses are often made clinically after assessing for a history of medication and product use and ruling out common infections including vulvovaginal candidiasis. Treatment is usually initiated empirically, and the majority of vulvar dermatoses are treated with topical corticosteroids. However clinicians should have a low threshold to obtain a biopsy in cases of unusual appearing lesions or in instances of treatment failure.

Disease prevalence, common symptoms, physical exam findings, recommended diagnostics, treatments, and prognoses of common vulvar dermatoses will be reviewed here. Given that many of these conditions can become recurrent or chronic, it is important that physicians remain mindful of the potential impact on patients' quality of life that these diseases can have and continue to work with patients to achieve good symptom control.

2 Vulvar Dermatoses

2.1 Contact Dermatitis

Contact dermatitis affects approximately 15–30 % of the population (Crone et al. 2000; Moyal-Barracco and Wendling 2014). Common causes of vulvar contact dermatitis are irritants and allergens. Fragrances, topical medications, and preservatives are the most frequent culprits (Hoang et al. 2014; O'Gorman and Torgerson 2013). Acute cases of contact dermatitis can present with erythema, edema, and even vesicles or erosions. Chronic contact dermatitis often presents as erythema with lichenified or excoriated areas. Patients complain of pruritus, pain, vulvovaginal dryness, burning, and dyspareunia (Fischer et al. 1995; Hoang et al. 2014).

Irritant contact dermatitis is the most common subtype. Factors including moisture from sweat or urine, heat, friction from clothing or scratching, estrogen deficiency, or enzymes can damage the skin's barrier properties and exacerbate irritation due to topical products (Margesson 2004; Moyal-Barracco and Wendling 2014). The list of potential irritants is extensive and essentially includes anything that comes in contact with the vulvovaginal region. Common irritants include soaps and detergents, dyes, perfumes, deodorants, lotions, condoms, spermicides, lubricants, sanitary products including tampons and pads, topical medications including anesthetics, antibacterials, antifungal preparations, corticosteroids, and bodily fluids including semen, saliva, and urine (ACOG 2008; Margesson 2004; Marren et al. 1992).

Allergic contact dermatitis is an immune-mediated type IV hypersensitivity reaction to an allergen which occurs in sensitized patients

(Margesson 2004; Moyal-Barracco and Wendling 2014). Numerous allergens have been identified; however, topical medications, including lidocaine, corticosteroids, and neomycin, as well as perfumes and metal such as nickel, are known to be causative agents (Marren et al. 1992; Moyal-Barracco and Wendling 2014). Patch testing in conjunction with a dermatologist can be considered if the etiologic agent cannot be identified (Crone and Stewart, 2000).

Patients with vulvar contact dermatitis often complain of burning or pruritus, and the course can be either acute or chronic. Poorly defined erythema is often noted on exam, and associated findings including edema, erosions or ulcers, and papules or vesicles can be found, especially in the area covered by diapers or sanitary napkins. If pustules or crusting are noted, a superimposed bacterial infection may be present. In chronic cases excoriation, changes in pigmentation and lichenification may be noted (Margesson 2004; Moyal-Barracco and Wendling 2014). On biopsy, contact dermatitis is characterized by histopathological findings of intraepidermal edema, spongiosis, acanthosis, parakeratosis, and infiltrating lymphocytes and eosinophils (Hoang and Reuter 2014; Moyal-Barracco and Wendling 2014).

In cases of contact dermatitis, use of all topical products should cease, and patients should use only water to clean the vulva. Resolution of symptoms is expected once the causative factor is removed. Patients may feel greater symptomatic relief with the addition of petrolatum for moisturization, and systemic antihistamines can be added for relief of pruritus (Margesson 2004; Moyal-Barracco and Wendling 2014).

2.2 Lichen Simplex Chronicus

Lichen simplex chronicus is a common dermatosis which causes severe vulvar pruritus. Initial symptoms may have been triggered by a topical irritant, candidiasis, moisture, heat, or friction, or concurrent lichen sclerosus (ACOG 2008; Virgili et al. 1997). Subsequent scratching alleviates the itch but damages the skin, over time resulting in a thickened epidermis which can appear leathery with areas of hyper- and hypopigmentation. Patients complain of a chronic recurrent pruritus, which often becomes worse at night. Frequent scratching results in erosions with accompanying pain and burning (ACOG 2008; Moyal-Barracco and Wendling 2014; Virgili et al. 2001).

Lichen simplex chronicus predominantly affects the hair-bearing skin on the labia majora. Skin often appears thickened and may be erythematous, pigmented, or pale, and excoriations are frequently noted. This condition often exhibits a chronic, relapsing pattern; however, it has not been associated with an increased risk of squamous cell carcinoma (Moyal-Barracco and Wendling 2014; Stewart 2010).

Potent topical corticosteroids are the mainstay of treatment for lichen simplex chronicus. Daily application for 3–4 weeks is recommended initially, followed by a taper or switch to a less potent topical steroid for the following 3–6 months to prevent recurrence (Lynch 2004; Moyal-Barracco and Wendling 2014). Topical calcineurin inhibitors such as tacrolimus or pimecrolimus ointment applied once or twice daily for 6 weeks, then tapered, are second line therapies for patients who do not tolerate or do not respond to topical corticosteroids (Goldstein et al. 2007; Moyal-Barracco and Wendling 2014).

2.3 Lichen Planus

Lichen planus is an inflammatory condition which can affect the vulvovaginal region as well as oral mucosa. The epidemiology of lichen planus is not well studied, but prevalence estimates range from 0.22–5 %, affecting both males and females (Gorouhi et al. 2014; Shiohara and Kano 2008). Vulvovaginal lichen planus most often affects peri- or postmenopausal women, though there have been reports of affected children (Gorouhi et al. 2014; McPherson and Cooper 2010).

Lichen planus is thought to be a T-cell-mediated inflammatory autoimmune disease. Studies have suggested possible genetic susceptibility as well as environmental triggers associated with lichen planus. Associations have also been noted

between lichen planus and coexisting stress, anxiety, and depression as well as hepatitis C infection, other autoimmune illnesses, dyslipidemia, and other viral infections (Gorouhi et al. 2014; Shengyuan et al. 2009; Vallejo et al. 2001).

Several subtypes of lichen planus have been described, based on morphology as well as the primary site of involvement (Gorouhi et al. 2014). Oral involvement is the most common subtype of mucosal lichen planus, with vulvovaginal involvement being the next most common and esophageal, laryngeal, and conjunctival involvement being rare (Eisen 1999; Gorouhi et al. 2014). In addition to affecting the mucous membranes of the mouth, vulvovaginal and anogenital region, gastro intestinal tract, conjunctiva, and mouth, lichen planus can affect the skin, nails, and hair. Among patients with vulvar lichen planus, 43–100 % also have oral lesions, and 25–57 % of patients who initially present for oral lesions are found to also have vulvar lesions (Belfiore et al. 2006; Eisen 1999; Gorouhi et al. 2014). Approximately 17–22 % of patients with vulvovaginal disease will also have skin lesions (Gorouhi et al. 2014, Simpson et al. 2012).

Lichen planus can have a variable appearance. Classic dermatologic presentations include the "6 Ps": "Pruritic, Purple, Polygonal, Planar, Papules, and Plaques" (Gorouhi et al. 2014; Lazar and Murphy 2009). When present on mucosal surfaces, the classic description is of white, lacy, or fernlike striae known as Wickham striae. Pruritic papules ranging in color from pink to violaceous can also be observed (ACOG 2008; Rogers and Eisen 2003).

Vulvovaginal lichen planus has three major subtypes: erosive, papulosquamous, and hypertrophic, with erosive being the most common (Gorouhi et al. 2014). Erosive vulvar lichen planus affects only the mucous membranes and can lead to vulvovaginal scarring, agglutination and resorption of the labia minora and clitoral hood, formation of synechiae, introital stenosis, and vaginal obliteration in extreme cases (Fig. 1). Affected women often complain of dyspareunia, burning, vaginal discharge, and postcoital bleeding and can have significant psychological distress due to the condition (Gorouhi et al. 2014; Lewis 1998).

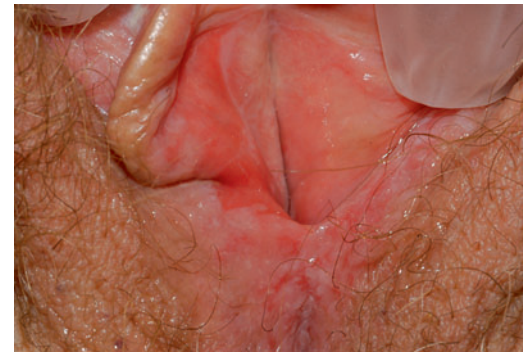

Fig. 1 A case of erosive lichen planus with early vaginal agglutination. (Reprinted from American Journal of Obstetrics and Gynecology, Vol 214, Issue 2, Fairchild PS, Haefner HK, Surgical management of vulvovaginal agglutination due to lichen planus, 289.e1-2, 2016, with permission from Elsevier)

Vaginal pH is frequently increased to 5 or 6 in lichen planus, and a wet mount often reveals numerous inflammatory cells as well as immature parabasal and basal epithelial cells (ACOG 2008; Rogers and Eisen 2003). Biopsy of the lesion confirms the diagnosis, and immunofluorescence staining can be used to distinguish between lichen planus and other similarly presenting immunobullous diseases. A dense continuous band of infiltrating lymphohystiocytes at the dermal-epidermal junction in the upper dermis is the classic histologic finding (Fung 2016; Gorouhi et al. 2014; Ramer et al. 2003). Other findings include hyperkeratosis, areas of wedge-shaped hypergranulosis, spongiosis in the spinous layer, squamatization, as well as elongated and rounded rete ridges. However, erosive vulvovaginal lichen planus can often have nonspecific histopathological findings, lacking the classic markers (Fung 2016; Gorouhi et al. 2014).

Topical application of super potent corticosteroids is the first-line treatment of vulvovaginal lichen planus with up to 55 % of patients experiencing symptomatic improvement with topical corticosteroids alone, while some patients will require oral therapy with prednisolone or a combination of topical and oral corticosteroids

(Schlosser and Microwski 2015). Topical corticosteroid therapy has been shown to be effective in treating symptoms including burning, pruritus, discharge, and dyspareunia; however the symptoms caused by vaginal stenosis were not significantly improved by topical corticosteroid therapy (Anderson et al. 2002; Schlosser and Microwski 2015). A variety of systemic immunomodulators have been studied with limited benefits observed and often with significant adverse effects noted. As such, systemic treatments are often limited to use for severe disease or refractory cases (Lotery and Galask 2003; Schlosser and Microwski 2015).

Vaginal dilators can be helpful in both treatment and prevention of adhesion and synechiae formation, which can occur in cases of inflamed, ulcerated vaginal mucosa. Dilators are often used in conjunction with topical corticosteroids, estrogen creams, or topical calcineurin inhibitors and can be used twice daily initially, then taped down to three times per week. Dilator therapy has been shown to be beneficial in helping patients resume sexual intercourse (Lotery and Galask 2003; Schlosser and Microwski 2015). In addition to dilators, use of vaginal hydrocortisone suppositories at a dose of 25 mg, initially used twice daily, then tapered down to twice weekly maintenance therapy, has been demonstrated to be effective for controlling symptoms of lichen planus (Anderson et al. 2002). If synechiae do form, surgical therapy should not be attempted until the inflammation due to lichen planus is well controlled. Lysis of adhesions and careful tissue dissection should be performed under general anesthesia, and vaginal dilators along with topical corticosteroids, with the addition of topical estrogen therapy in certain cases, must be used during the healing process to prevent scarring and additional adhesion formation (Kortekangas-Savolainen and Kiilholma 2007; Schlosser and Microwski 2015).

Regarding prognosis, cutaneous lichen planus can resolve in about 6 months to 1 year; however some types of oral lichen planus can become chronic and progressive. Erosive lichen planus, which is the most common subtype affecting the vulvovaginal region, can display a chronic, waxing and waning, cyclic pattern. Risk of malignant transformation of lichen planus has been suggested, but studies have been inconclusive, and further study is required (Cooper et al. 2004; Gorouhi et al. 2014).

2.4 Lichen Sclerosus

Lichen sclerosus is one of the most common inflammatory dermatoses of the vulva. It is a chronic autoimmune inflammatory condition affecting the vulvovaginal region, thought to be mediated by lymphocytes. It is more common in women than men (Schlosser and Microwski 2015). Lichen sclerosus exhibits a bimodal age distribution. It occurs commonly in prepubertal girls with a prevalence of 1 in 900 and a mean onset at 5 years of age. Perimenopausal to postmenopausal women are usually affected between ages 45 and 55; however, it can also present in women of reproductive age. There is often a delay in diagnosis of approximately 2 years in young patients and 5–15 years in older women. Cutaneous lesions outside of the genital region can be present in 6–15 % of patients affected by lichen sclerosus (Cooper et al. 2004; Schlosser and Microwski 2015).

Reports suggest a familial predisposition, though the mode of inheritance has not been identified. Several genes have been studied with possible protective as well as predisposing genes under investigation. There is also a significant link between lichen sclerosus and autoimmune disorders, including autoimmune thyroid disease, as well as vitiligo, alopecia areata, pernicious anemia, and diabetes mellitus, among others (Meyrick et al. 1988; Schlosser and Microwski 2015). Additionally the role of estrogen and androgens in lichen sclerosus has been investigated but remains a subject for further study (Schlosser and Microwski 2015; Taylor et al. 2008).

Patients commonly present with vulvar pruritus which can be more severe at night. They can develop painful vulvar and perianal erosions and fissures which lead to dysuria, dyspareunia, and dyschezia. Patients can develop urinary retention and constipation secondary to pain. As such, stool

retention is commonly the presenting symptom of lichen sclerosus in young girls. Disease progression and labial agglutination are concerns for young girls diagnosed with lichen sclerosus, and abnormal voiding with weak urinary stream can result from labial agglutination (Powell and Wojnarowska 2001; Schlosser and Microwski 2015).

Lichen sclerosus typically affects the labia majora and minora, clitoris and clitoral hood, and the posterior fourchette. The perianal area is affected in 30–60% of women, often with a classic hourglass or "figure of eight" pattern when both the vulva and perianal region are affected. The vaginal mucosa is usually spared. A white, hypopigmented vulvar skin with a waxy or wrinkled texture, classically described as appearing like "cigarette paper," is the typical clinical exam finding. Patients may also have fissures, erosions, and ulceration as well as hyperkeratosis or purpura, and clitoral hood edema (Schlosser and Microwski 2015; Virgili et al. 2014). Scarring can occur to varying degrees, most commonly affecting the clitoral hood and labia minora as well as the posterior fourchette and introitus (Fig. 2). Resorption of the labia minora has been observed, and scarring can result in stenosis of the vaginal introitus or urethral meatus to the point that intercourse and voiding are impaired. Lichen sclerosus can also result in areas of hyperpigmentation which can be difficult to differentiate from potential melanoma, and as such, biopsy is recommended. Extragenital lesions in cutaneous lichen sclerosus can also be observed and predominantly affect the trunk, though rare cases affecting the face, scalp, mouth, and nails have been reported (Schlosser and Microwski 2015).

Treatment with topical corticosteroids is recommended if clinical signs are suggestive of lichen sclerosus. Biopsy is indicated if lesions do not respond to topical therapy; if there is concern for malignancy, including melanoma; or if ulcerated lesions are present (Schlosser and Microwski 2015). Hyperkeratosis, an atrophic epidermis, loss of rete ridges, and band-like lymphocytic infiltrate are classic histopathological signs of lichen sclerosus (Schlosser and Microwski 2015).

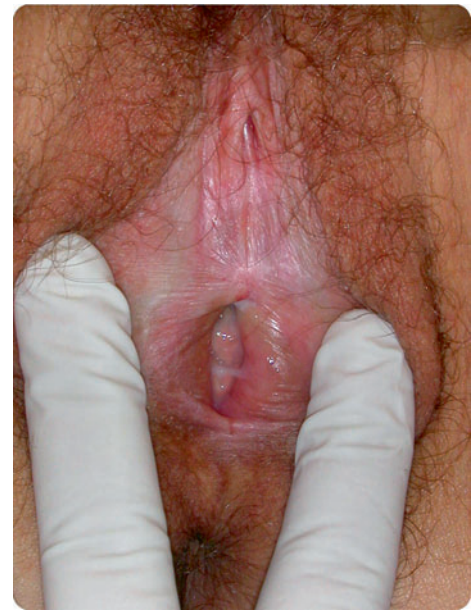

Fig. 2 Scarring of the vulva from lichen sclerosus. (Reprinted from the American Journal of Obstetrics and Gynecology, Vol 196, Issue 2. Goldstein AT, Burrows LJ. Surgical treatment of clitoral phimosis caused by lichen sclerosus, 126.e1-4, 2007, with permission from Elsevier)

Lichen sclerosus is associated with a nearly 300 times increased risk of development of vulvar squamous cell carcinoma, with a period of 4–10 years between diagnosis of lichen sclerosus and diagnosis of vulvar squamous cell carcinoma. It is unclear if successful treatment of vulvar lichen sclerosus decreases the risk of vulvar squamous cell carcinoma; however, carcinoma is seen typically in elderly patients and has not been reported in pediatric patients. Age greater than 70 years has been associated with treatment failure and disease recurrence (Carli et al. 1995; Schlosser and Microwski 2015).

Topical treatments in ointment formulations are preferable as they have improved potency and absorption. Ointment formulations also have emollient properties and are less likely to contain vulvar irritants including preservatives, alcohol, and propylene glycol. Topical superpotent corticosteroids are the mainstay of therapy for vulvar lichen sclerosus, and clobetasol propionate 0.05 % ointment has demonstrated significant efficacy in randomized trials (Schlosser and

Microwski 2015). An initial twice-daily application is recommended. As symptoms improve, the application can be tapered and a less potent corticosteroid can be used. Maintenance therapy over a period of 6–12 months is commonly recommended. Side effects of long-term topical corticosteroid therapy include atrophy and thinning of the skin as well as development of striae and telangiectasias. Long term use can also increase susceptibility to superimposed candida infections and can be associated with reactivation of herpes simplex viral infection (Schlosser and Microwski 2015).

Topical estrogen therapy may be beneficial in postmenopausal patients who experience significant atrophy with topical corticosteroid use. In addition, oral antifungals and antihistamines can be used to combat side effects rather than utilizing their topical formulations. Topical creams may exacerbate symptoms due to their potential to act as topical irritants. Second-line therapy includes a twice-daily application of topical calcineurin inhibitors, such as tacrolimus 0.1 % ointment, which may be chosen for use in cases which demonstrate a lack of response to topical corticosteroids or in patients who develop side effects from corticosteroid therapy; however, their use has been associated with a reportedly increased risk of dermatologic malignancies (Fischer and Bradford 2007; Schlosser and Microwski 2015).

Systemic retinoid therapy such as acitretin can be useful for patients with hyperkeratotic or hypertrophic vulvovaginal lichen sclerosus refractory to superpotent topical corticosteroids. Oral acitretin regimens of 20–30 mg per day over a course of 16 weeks have been studied; however, as retinoids are teratogenic, they should not be used in women who might become pregnant. There is evidence that acitretin can reduce the incidence of squamous cell carcinoma in at-risk patients such as those who have undergone organ transplantation. It is suggested that there may also be a similar protective effect against squamous cell carcinoma in patients with lichen sclerosus; however, further study into this area is necessary (Bousema et al. 1994; Schlosser and Microwski 2015).

Surgical therapy for severe vulvar and introital scarring affecting function should only be undertaken after resolution of inflammation with at least a 6-month, disease-free period. Superpotent topical corticosteroids must be used to prevent a postoperative lichen sclerosus recurrence due to the Koebner phenomenon (the development of new lesion areas secondary to trauma) as well as to prevent recurrence of labial agglutination and stenosis of the introitus (Schlosser and Microwski 2015).

Additional supportive measures can be undertaken to help manage the pruritus, pain, and irritation. Patients should wash the vulvar area with water only, then pat dry and avoid rubbing. Sitz baths as well as ice packs and cool compresses can be utilized to ease burning symptoms. Petroleum jelly or A and D ointment can act as soothing emollients and decreases friction in the affected areas. Some patients develop a secondary vulvodynia which may be treated with topical 5 % lidocaine ointment, while other patients may benefit from systemic treatments for neuropathic pain including amitriptyline and gabapentin (Schlosser and Microwski 2015).

In most patients disease control should be attained within 3–4 months. Patients should then be followed every 6–12 months to monitor for disease recurrence as well as for the development of atrophy, scarring, or potential malignant changes. Cases that do not improve despite appropriate therapy should be reassessed, and alternate diagnoses such as contact dermatitis, a superimposed infectious process, or undiagnosed malignancy should be considered and further evaluated. Suspicious or unresponsive areas must be biopsied. A multidisciplinary approach should be considered for patients with refractory or multifocal disease as well as to help manage common psychological effects secondary to severe or persistent disease (Schlosser and Microwski 2015).

2.5 Psoriasis

Vulvar psoriasis affects approximately 5 % of women and 15 % of girls with vulvar dermatosis.

This chronic dermatosis is generally diagnosed clinically and has several presentations, including the classic form with well-demarcated thick scaly plaques, discrete pustules in the pustular form, or as erythema with minimal scaling in the inverse form which presents predominantly in the anogenital area and in flexural folds. Vulvar psoriasis affects the hair-bearing cutaneous regions of the vulva, especially the mons pubis and labia majora, and generally spares the mucosa (Hoang et al. 2014; Kapila et al. 2012). Biopsy frequently is nondiagnostic, however areas of parakeratosis with neutrophils, known as Munro's microabscesses, as well as spongiosis are a common finding (Hoang et al. 2014).

Treatment of vulvar psoriasis should focus on relief of symptoms and the minimization of Koebnerization. Use of soothing emollients and avoidance of topical irritants is recommended. Flares can be managed with topical mid- to high-potency topical corticosteroids. Topical corticosteroid therapy can then be followed with topical tar preparations, retinoids, calcineurin inhibitors, and low potency topical corticosteroids for maintenance therapy. In rare cases of severe refractory disease, systemic therapy with methotrexate may be considered; however limited efficacy has been demonstrated with this treatment (Kapila et al. 2012).

3 Neoplasms

3.1 Vulvar Intraepithelial Neoplasia

Vulvar intraepithelial neoplasia (VIN) is a premalignant squamous lesion with a peak incidence of 5 per 100,000 women which is observed primarily in Caucasian women in their forties (Preti et al. 2014). VIN was historically divided into three grades. However, after studies revealed that VIN 1 was predominantly a self-limited disease due to human papillomavirus (HPV) infection, the International Society for the Study of Vulvovaginal Disease (ISSVD) revised the classification system in 2004 such that now only a high-grade disease is classified as VIN, and what was previously called VIN 1 is now classed and treated as condyloma (Sideri et al. 2005). VIN is now subdivided into usual-type VIN and differentiated VIN. Usual-type VIN is the most common type and is linked to carcinogenic HPV genotypes as well as states associated with persistent HPV infection including being immunocompromised and smoking. This grouping includes warty, basaloid, and mixed VIN. Differentiated VIN accounts for only 2–5 % of cases of VIN. It is more commonly associated with vulvar dermatoses such as lichen sclerosus, a risk factor for squamous cell carcinoma, and is not associated with HPV infection (Preti et al. 2014; Sideri et al. 2005).

There is no screening test specifically for VIN, which is diagnosed clinically. VIN has a variable presentation. Color can range from gray or white to red, brown, or even black. The majority of lesions are raised (Fig. 3); however, they can be flat as well. Vulvar colposcopy can be used to aid visual inspection of the area after applying cotton pads soaked with 3–5 % acetic acid. Any suspicious or pigmented lesion, any areas refractory to treatment, or lesions found in a postmenopausal woman should be biopsied (ACOG 2011; Preti et al. 2014).

All cases of VIN should be treated. If malignancy is suspected, VIN lesions should be surgically managed with wide local excision, using either a cold knife or loop electrode excision. In rare cases, such as in immunocompromised women with extensive disease, a skinning vulvectomy may be considered. Gross margins of 0.5–1 cm are preferred when performing wide local excision, though adjustments can be made to avoid structures such as the urethra, clitoris, and anus. Negative margins on pathologic examination are preferred, however risk of recurrence remains. If suspicion for malignancy is low, CO_2 laser ablation or topical therapy with imiquimod 5 % for 12–20 weeks, cidofovir 1 %, or photodynamic therapy in conjunction with the photosensitizing agent 5-aminolevulinic acid (ALA) can be utilized (ACOG 2011; Preti et al. 2014).

The quadrivalent HPV vaccine reduces the risk of developing VIN as it confers protection from HPV genotypes 6, 11, 16, and 18 (Muñoz et al. 2010). Smoking cessation should be

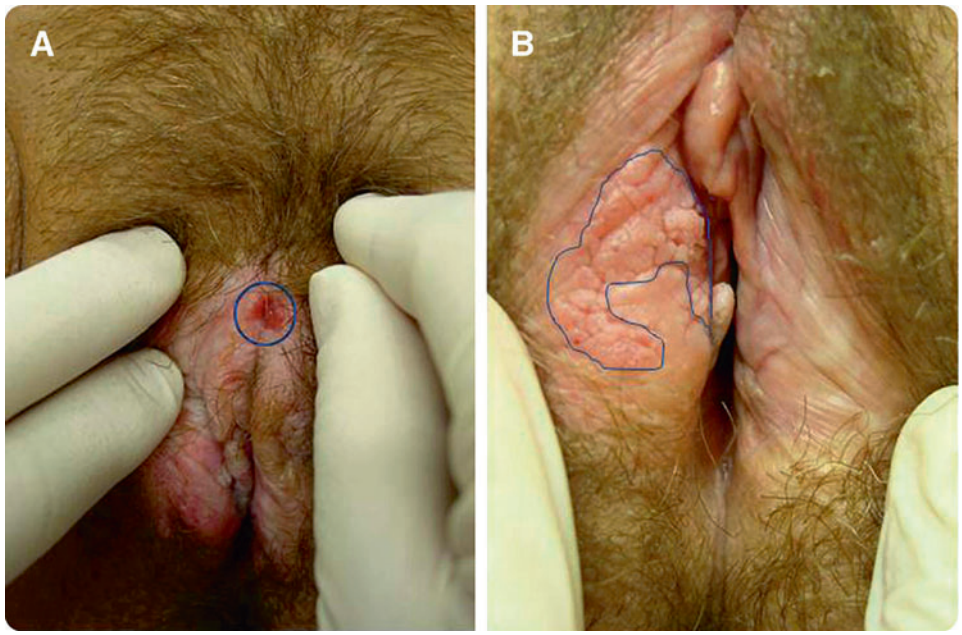

Fig. 3 (**a**) Vulvar SCC on the left labium minus, 9 mm diameter and with a depth of invasion of 4 mm. (**b**) Lesion on the right labium minus, which turned out to be VIN on histologic examination. (Reprinted from American Journal of Obstetrics and Gynecology, Vol 203, Issue 2, Simons M, Van De Nieuwenhof HP, Van Der Avoort IA, Bulten J, De Hullu JA, A patient with lichen sclerosus, Langerhans cell histiocytosis, and invasive squamous cell carcinoma of the vulva, e7-10, 2010, with permission from Elsevier)

stressed, as it is associated with usual-type VIN, and the diagnosis and treatment of vulvar dermatoses may reduce the risk of differentiated VIN and development of squamous cell carcinoma (ACOG 2011).

Despite treatment, recurrence rates can be as high as 30–50 %, and rates are even higher if positive margins were noted on excision. After treatment, patients should be re-examined at 6 months and 1 year and can then resume yearly monitoring if no new lesions are noted (ACOG 2011), though some studies suggest following patients more closely, with follow-up every 3 months for the first 2–3 years, then every 6 months subsequently (Preti et al. 2014).

4 Conclusion

As reviewed above, numerous conditions can manifest as vulvar disease. When evaluating vulvar complaints, a thorough history and physical examination are essential, as well as an awareness of the wide range of potential diagnoses. The first steps in evaluation often involve assessment for and removal of potential irritants as well as testing for suspected infections. Discontinuation of topical products is often a crucial component in the management of symptoms, as nearly any product in contact with the vulvovaginal region has the potential to cause irritation.

The common dermatoses reviewed in this chapter, including contact dermatitis, lichen simplex chronicus, lichen planus, lichen sclerosus, and psoriasis, are often treated with topical corticosteroids as a first-line therapy. However, providers should have a low threshold to obtain a biopsy for tissue diagnosis in refractory cases or unusual presentations in order to rule out underlying malignancy or alternate diagnoses.

In severe and chronic cases of vulvar dermatoses, a long-term follow-up is often indicated to monitor for disease recurrence or progression, potential malignant transformation, as well as

vulvovaginal scarring, labial agglutination, or introital stenosis. Cases of VIN must be monitored closely due to high rates of recurrence as well as risk of malignancy.

Depending on the etiology of the vulvar disease, patients may have multifocal disease affecting more than one organ system. As such, a multidisciplinary approach should be taken to coordinate therapy. Additionally, patients can experience significant morbidity from vulvar dermatoses, which may have wide impacts on various activities ranging from normal sexual activity to basic voiding function. These morbidities can have significant psychological impacts on patients which should be addressed as a component of comprehensive gynecologic care.

5 Cross-References

- Benign Vulvar and Vaginal Pathology
- Diagnosis and Treatment of Vulvovaginitis
- Management of Chronic Recurrent Vulvovaginitis
- Management of Vaginal and Vulvar Lesions in the Older Woman
- Pre-invasive Epithelial Disease of the Vulvar

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Management of Vulvodynia

Martha Goetsch

Contents

Abstract

Vulvodynia is the term assigned when a woman has a chronic condition of pain in the inner or outer vulva that has lasted longer than 6 months and cannot be explained by a chronic skin condition or infection. The general diagnostic term vulvodynia is used to describe two subtypes of vulvar pain. One is localized to the vestibule of the vulva, generally is painful only when touched, and is the most common explanation for repeated pain at initial vaginal penetration. It is the most common form of vulvodynia, termed localized provoked vulvodynia (LPV). The second form of vulvodynia causes a constant burning sensation in areas of the outer vulva, whether touched or not, and is less common. Vestibular vulvodynia is often associated with tight pelvic floor muscles and was initially described in 1861 by Marion Sims and named vaginismus. Localized provoked vulvodynia has characteristic histologic findings of nerve hyperplasia and an infiltrate of lymphocytes and mast cells. A multitude of therapies has been tried for both types of vulvodynia, but careful comparative studies have been few. Because of the significant associated problem of dyspareunia, this condition has very deleterious effects on intimacy, development of relationships, and self-image. Therapeutic efforts should be multidisciplinary, including gynecologic assessment and treatment of local skin pain, physical therapy to retrain tight pelvic floor

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muscles, and skilled mental health counseling for emotional difficulties.

Keywords
Vulvodynia • Localized provoked vulvodynia • Generalized vulvodynia • Dyspareunia • Female sexual pain • Chronic vulvar pain condition

1 Introduction

Vulvodynia has been a puzzling disorder with a checkered history of varying understandings, explanations, therapies, and research initiatives. It may be one of the most interesting of misunderstood medical conditions. Because localized provoked vulvodynia is a cause of repeatedly painful sexual intercourse affecting 12–14 % of women in the premenopausal population, all care practitioners who see women should be conversant about vulvodynia and vulvar conditions in general. With steadily increasing ease of finding information using electronic search engines, more and more women are assigning a potential name to their own pain condition and then requesting help from their gynecologist. Additionally, pressure at the National Institutes of Health (NIH) to increase vulvodynia research funding has been increasing. Finally, as the population bubble of older women swells and as women have increasingly stopped using supplemental estrogen in postmenopause, there is evidence that the very prevalent problem of postmenopausal dyspareunia is a form of localized provoked vulvodynia.

2 Nomenclature of Vulvodynia

In 2015 three specialty organizations produced a consensus document of terminology and classifications of persistent vulvar pain. The organizations were the International Society for the Study of Vulvovaginal Disease (ISSVD), the International Society for the Study of Women's Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS).

"**Vulvodynia** is vulvar pain of at least 3-month duration, without clear identifiable cause, which may have potential *associated factors*."

Categories are further defined by descriptors:

- Localized (e.g., vestibulodynia, clitorodynia) or generalized or mixed (localized and generalized)
- Provoked (e.g., insertional, contact) or spontaneous or mixed (provoked and spontaneous)
- Onset (primary or secondary)
- Temporal pattern (intermittent, persistent, constant, immediate, delayed)

Associated factors are often "musculoskeletal," such as pelvic floor myalgia; "psychosocial," with feelings of inadequacy, grief, anxiety; or "comorbidities" such as painful bladder syndrome or fibromyalgia.

Allodynia is a painful sensation from a stimulus that should be painless. This is in contrast to hyperalgesia, which is enhanced intensity of a pain sensation.

The most common form of vulvodynia is localized provoked, and it is often referred to as vestibulodynia since it is localized to the vulvar vestibule. Studies have suggested that this form occurs in 90 % of those diagnosed with vulvodynia. The less common form of vulvodynia is generalized vulvodynia, which usually has a spontaneous and constant level of pain and describes 10 % of those with vulvodynia (Lamvu et al. 2015).

2.1 Anatomy

The vulva has distinct zones because of embryologic origins. The tissues comprising labia majora and minora are derived from ectodermal tissues and have an array of potential problems that must be ruled out in an assessment of vulvar pain. For instance, the dermatosis of lichen sclerosus is an inflammatory disorder that affects the ectodermal skin primarily.

The vulvar vestibule is a second distinct zone comprising mucosa from the inner labia minora to

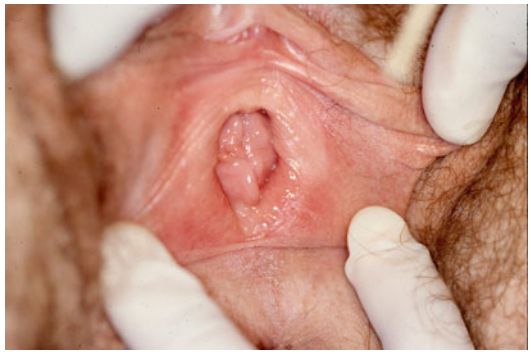

Fig. 1 The vestibule is the area medial to Hart's line, seen here as the demarcation between somewhat ruddy coloration and a pale zone along the inner surface of the labia minora. The lateral labial tissue is of ectodermal origin and the pale zone is endodermal in origin. The vestibule extends from Hart's line to hymen and fourchette to clitoris (Goetsch 1996)

the hymen and from just under the clitoris to the fourchette. This introital zone is endodermal in embryologic origin, perforated by the urethra and related to the bladder in development. The demarcation of the ectodermal and endodermal zones is Hart's line, named after an Edinburgh gynecologist in the 1880s who noted the visual landmarks. Figure 1 shows these landmarks with Hart's line visible midway along the inner aspect of the labia minora. This vestibular zone of mucosa forms the entryway to the vagina, and the vestibule is supposed to be sensitive in a positive way, but has a capacity to develop localized exquisite tenderness, i.e., vulvar vestibulodynia, or become very symptomatic from an inflammatory trigger such as *Candida.*

The structure representing the innermost point of the vulva is the hymen where the vaginal mucosa begins, and the vaginal mucosa is mesodermal in origin. Therefore, within about 1.5 in., three embryologic layers are represented. Each zone has different and unique tissue properties including different nerve sensitivities.

Some systems of *nomenclature* refer to vulvar pain as a subcategory of pelvic pain. This can be confusing since the common clinical problem associated with vulvodynia is pain with intercourse and specifically pain at first penetration. Vulvodynia is vulvar pain, not deeper pain from the pelvis. Dyspareunia is a term derived from the Greek words for "badly mated". It is important to distinguish entry dyspareunia, which is pain occurring at initial penetration, from deep dyspareunia, associated with deep penetration of the vagina. The vagina itself does not usually account for pain in various female genital pain syndromes. Compared to the severity of typical introital symptoms of pain or itching or the severity of upper tract pain from uterine/tubal/abdominal structures, the vagina is relatively nontender. Structures just deep to the vaginal walls can be tender and will be discussed below. Causes of deep pelvic pain can be conditions such as adenomyosis, endometriosis, or pelvic scarring from prior infections or surgery. Vulvar pain might reasonably be segregated from pelvic pain in pain classifications.

Another consideration regarding nomenclature is the difference between "chronic pain" and a "chronic condition" that causes intermittent pain. Localized provoked vulvodynia is a cause of exquisite pain on touch, as, for example, with repeated penetrative activity of intercourse. However, if a woman with this chronic condition refrains from intercourse, she may well have no pain. Generalized vulvodynia, on the other hand, is a condition of persistent spontaneous pain that is sometimes completely unremitting.

The origin of -dynia is from the Greek *οδύνη* (odunē, "sorrow, grief, anguish, unhappiness"), which is used as a term meaning "painful." Women's descriptions of vulvodynia are usually those of a thermal nature. Generalized vulvodynia usually has a burning or stinging sensation, and localized vulvodynia has a burning, raw, or tearing sensation provoked by entry penetration.

Generalized vulvodynia is an acquired condition. In contrast, the more common condition, localized provoked vulvodynia (LPV), is categorized by onset as either primary or secondary. The primary type will have been present with penetrative attempts for as long as the patient can recall – often from the first attempt to place a tampon, the first attempt at coitus, and the first speculum examination. This implies a presence before recognition, perhaps even since childhood, but there is not a body of information about prepubertal

girls since genital examinations are restricted in this age group so as not to cause emotional harm. Secondary vestibulodynia is a penetrative pain that has been acquired after there has been no prior pain with penetration.

3 Taking a Patient History

For **localized provoked vulvodynia** (LPV), the usual patient complaint is pain with penetration. On taking a history, it is useful to ask about qualities of pain, timing of onset, and other associated issues. The pain is usually described as burning or tearing in nature. If milder, it is described as an irritation as if tissues are dry. The use of a lubricant can help in more minor cases but does not correct severe tenderness. Ask patients when they first experienced pain with sex, but questions about other examples of penetration are useful. Attempts with tampons usually antedate the first speculum examination or first coital attempts by years indicating early presence of the disorder. Removal of an engorged tampon is often more painful than insertion. Those with severe LPV often cannot use tampons due to pain.

A clinical history should allow an assignment to primary versus secondary status, although the plan of therapy does not depend on the LPV type. *Comorbidities* such as psychosocial impairment are more common in women with primary LPV who have never known painless intimacy and often come to attention later than women with secondary LPV. The *duration* of time women have been suffering pain and continuing to have intercourse will also affect the likelihood that they have developed the secondary problem of pelvic floor myalgia as a reaction to entry pain. *A family history* may reveal a mother or sisters who have had a similar pain condition, but this very private information may not have been shared. Finally, it is useful to ask about *bladder issues* such as frequency, urgency, and nocturia as patterns that may reveal the comorbidity of bladder involvement either because of mucosal inflammation or due to tight pelvic muscles reducing filling capacity.

4 Differential Diagnosis

Vulvar pain and dyspareunia can be caused by other vulvar or genital problems than vulvodynia. Infections should be ruled out before the diagnosis of vulvar vestibulodynia is assigned. Such problems can also be comorbidities with vulvodynia, however, so if treatment of the obvious problem does not return a patient to normal, the differential diagnosis should be expanded with a consideration of vulvodynia. Many vulvar pain sufferers have been to multiple practitioners before they get an accurate diagnosis, and they often give histories of having been treated multiple times with antifungals or antibiotics for a presumed vaginitis. Whereas it is true that a vaginitis such as candidiasis or an irritative bacterial vaginitis (desquamative inflammatory vaginitis) creates acute symptoms in the introitus, these symptoms will clear with appropriate therapy. Without evidence of a vaginitis on visual or microscopic examination, vaginal pathogens are an unlikely cause of introital pain symptoms. Of note, bacterial vaginosis (BV) is an imbalance of vaginal bacteria and not a cause of pain, typically causing just an odor ("halitosis" of the vagina?) and/or discharge. BV is too often blamed for the pain condition of vulvodynia, leading to inappropriate and ineffectual antibiotic use and delay in accurate diagnosis.

An exception to the accuracy of standard office microscopy is subclinical *Candida albicans* or *Candida glabrata*, due to vaginal colonization which causes vestibular symptoms. These pathogens can be diagnosed with the DNA probe or vaginal culture. In the case of candida, oral antifungal treatment for a series of a few weeks can reestablish a baseline of normal vulvar sensations to assess that there is not a component of vulvodynia that is present.

Dermatologic conditions of the vulva and vagina (lichen planus, LP, and lichen sclerosus, LS) can cause pain with intercourse. If vulvar scarring is noted, an inflammatory process is to blame, not vulvodynia or atrophy. In the setting of visual changes in the vulva, a biopsy may be indicated. A routine biopsy (with LS) or

immunohistochemical staining (with LP) can establish the diagnosis unless the physical appearance is sufficient to classify the dermatosis. These inflammatory processes require steroid therapy for control.

5 Physical Examination of Vulvodynia

Vulvodynia is often described as a diagnosis of exclusion with no physical findings. This is the case with generalized vulvodynia, but not with localized provoked V. Care in doing a focused examination of the external vulva and vestibule is primary. First, the patient should be asked to clarify where she feels pain, pointing and touching the specific areas. A simple examination of the *external* vulva employs light probing touch by the examiner's finger and can ascertain whether pain is elicited. A swab touch test of the *vestibule* can then be performed, mapping the degrees of pain in specific zones.

Findings in generalized vulvodynia: Pain is usually in areas outside the vestibule, thereby distinguishing it from vestibulodynia. Locations can be confirmed by touch, but touch does not always provoke more pain during the examination process. There are no visual skin changes.

Findings in localized provoked vulvodynia: The labial tissues must be gently but firmly drawn far enough apart to examine the entire vestibule including the crypts next to the hymen, especially at each Bartholin's duct orifice. In normal settings light touch in this zone is not tender. Allodynia is tenderness to types of touch that should not be painful, and this characterizes vestibulodynia. A physical finding of erythema is usually evident in portions of the vestibule. Redness can be very specific to the zone of allodynia, for instance, forming a U-shape from 3 to 9:00, as if the hymen were a clock face. The most pronounced redness is often around each Bartholin's duct orifice. Reddened spots can exist at tiny vestibular gland openings in the anterior vestibule. The erythema is not an erosion or ulcer but is from dilation of fine capillaries. General redness *without* tenderness is a physiologic variant and not of concern.

The "swab test" utilizes a small cotton-tipped applicator moistened with water. The locations of pain are mapped using light rolling touch checking all surfaces of the vestibular mucosa. This technique reflects observations about this condition from an old text from 1885 stating that "the touch of a feather is insupportable." The scoring can be 0–3: 0 = nontender, 1 = annoying touch, 2 = stinging or burning sensation, and 3 = very painful touch causing patient to flinch.

Some authors have utilized an **algesiometer** in research settings (Pukall et al. 2003). It measures the threshold of pain using calibrated swab pressure or calibrated touch with von Frey hairs. It should be noted that prodding actions will also impact submucosal tissue layers; poking maneuvers may inadvertently elicit pain from superficial submucosal structures like muscles. Therefore light, rolling touch of a cotton swab may be preferable and sufficient to examine mucosa. Algesiometers or vulvalgesiometers are not readily available and the cotton swab therefore provides a simple tool for all practitioners to use.

The "lidocaine test" helps to establish the mucosal nature of LPV because the application of aqueous 4 % lidocaine for 1–3 min can extinguish the mucosal pain of LPV but does not ablate the pain of aberrant nerve function in centrally mediated generalized vulvodynia (see "Histology and Theories"). Both localized vulvodynia (vestibulodynia) and generalized vulvodynia can be present in a mixed form in the vestibule and outer vulva, although this is not the usual circumstance.

Some women are so avoidant of an exam of the vestibule that touch is not possible on the first visit. This has confounded the elucidation of "vaginismus," since women have been entered into studies without having undergone full examinations for the mucosal pain condition of LPV (Reissing et al. 2004).

Lidocaine is extremely helpful in examining women with other causes of mucosal tenderness, like vulvitis or a lichenoid dermatosis. Quelling introital tenderness makes it possible to accurately examine upper genital structures without eliciting

pain from the introitus from touch with fingers or a speculum.

6 Histology and Physiology of Vulvodynia

No histologic changes have been documented in generalized vulvodynia. It is considered a condition of aberrant nerve function with central sensitization with no specific nerve abnormalities at the peripheral skin level. Biopsies are negative for pathology.

Histologic studies of vestibulodynia (localized provoked vulvodynia) have found an excessive number of nerve endings in the vestibule mucosa and submucosa (Bohm-Starke et al. 1999). These nerves are pain nerves (nociceptors) that are the type targeted by local anesthetic agents such as lidocaine that block sodium channels. Additionally, the local neural hyperplasia is accompanied by an infiltrate of lymphocytes and mast cells. The lymphocytes have been characterized as T-cells, and the inflammation is not the type responsive to therapy with topical steroids (Bohm-Starke et al. 2001).

Differences in degree of neural hyperplasia and lymphocytic infiltrate have been noted in different types of vestibulodynia. Nerve trunks and mucosal branches are most pronounced in tissues from women with primary LPV (Leclair et al. 2011). The lymphocytes are more numerous in tissues from women with secondary LPV, with the most marked lymphocyte infiltrates in postmenopausal women's tissues (Leclair et al. 2013).

Vulvodynia does not predispose to cancer and is not contagious.

7 Population Findings in Vulvodynia

Premenopausal vulvar vestibulodynia: Several prevalence studies have established that 12–14 % of young premenopausal women have LPV (Harlow et al. 2014). There are an equal proportion of sufferers in primary and secondary categories. Localized provoked type comprises 90 % of cases of vulvodynia (Lamvu et al. 2015). Women have typically consulted five clinicians about their problem before receiving an accurate diagnosis.

Postpartum vulvar vestibulodynia: Postpartum dyspareunia is a poorly studied phenomenon, but one prospective study found that 37 % of women delivering babies developed introital pain with penetration in association with lowered hormones after delivery and during lactation (Goetsch 1999). The women's complaints were similar whether their delivery had been vaginal or abdominal. The severity was equally apportioned between mild, moderate, or severe pain, and median duration was 5 months. For some women postpartum dyspareunia does not resolve with the return of natural estrogen and periods. Two prevalence studies have found that 25 % of women with vestibulodynia described the onset as postpartum. It is unknown how many women need to deliver for one to develop chronic long-term vestibulodynia.

Generalized vulvodynia: Population studies indicate that there is a stable prevalence of 8.3 % of vulvodynia through age 70. For about 17 %, however, symptoms may begin or remit spontaneously (Reed et al. 2012). Early studies termed this condition "essential vulvodynia" and described it as a complaint of postmenopausal women with constant sensations of irritation or stinging. It can be a comorbidity in younger women with LPV and can develop rarely after a vestibulectomy. A large clinical study indicated that 10 % of women with vulvodynia have generalized type (Lamvu et al. 2015).

Postmenopausal pain with sex: Dyspareunia is very common in postmenopause and has suffered from a lack of research (Kao et al. 2008). There has been a hesitation to consider postmenopausal dyspareunia to be vulvodynia since the definition states "without another identifiable cause," and in this age group, pain has commonly been ascribed to atrophy causing vaginal dryness. The newer term is genitourinary syndrome of menopause (GSM) and replaces the term "vulvovaginal atrophy" (Portman and Gass. 2014). GSM includes symptoms of dyspareunia, sensations of dryness, and urinary and vulvar irritation. Atrophy is a condition of thinned genital

tissues from the lack of estrogen that characterizes menopause. Without estrogen, the uterus and cervix shrink, and vaginal, vestibular, and outer vulvar tissues thin. A problem with attributing menopausal dyspareunia to atrophy is that the intimacy tenderness is localized to the vestibule and not the vagina, despite both having developed atrophy (Goetsch et al. 2014). Additionally, not all women with genital atrophy have dyspareunia. Finally, in other circumstances of physiologic atrophy, such as muscle atrophy, there is no associated pain condition. For these reasons there is pressure to reconsider the definitional injunction against labeling a condition vulvodynia if the "clear identifiable" associated cause is atrophy (Kao et al. 2008). In women with menopausal dyspareunia, an examination indicates that the pain is at the entryway and is tenderness, not dryness. The use of lubricants can temper the sensation of irritation or pain, but they do not remove pain as should be expected if this were simply dryness. The use of lubricants is a good idea in menopause generally, for reasons of less natural lubrication, and a silicone lubricant is a good option.

Postmenopausal dyspareunia fulfills the criteria of being localized to the vestibule and only painful when provoked, similar to the condition of vestibulodynia found in younger women. Menopausal vulvar vestibulodynia can be diagnosed with the cotton swab and lidocaine tests, demonstrating that there is extinguishable mucosal pain and no other cause of penetrative tenderness as demonstrated by a painless speculum examination.

The lack of estrogen in menopause can therefore cause two concomitant problems: vestibulodynia and general genital atrophy. Estrogen therapy usually corrects both conditions, but not uniformly. For localized therapy the instructions are to apply estrogen into the vagina. However, this does not directly treat the important location of the vestibule, and low-dose vaginal therapy may not be strong enough to correct vestibular tenderness.

Another example of chronic vulvar pain may be emerging now that years have passed after women were urged in national guidelines to forego postmenopausal estrogen. Women are presenting in the later years of menopause who have constant burning pain arising from the vestibule. These women often have not used estrogen for years or they have used special antiestrogen medications (such as aromatase inhibitors) as treatment for breast cancer. Their burning pain is constant and debilitating. It is a very severe example of vestibulodynia and responds to estrogen therapy directed to the vestibule (Goetsch 2012).

8 Theories of Causation of Localized Provoked Vulvodynia

Current research is pursuing various possible triggers for both primary and secondary vulvar vestibulodynia.

Scarring was an early theory to explain dyspareunia. It was proposed by Woodruff, who suggested that submucosal scarring from childbirth was causative. He demonstrated that a surgical procedure could be quite palliative, but because he believed scars to be the cause, his procedure advanced vaginal tissues out over the fourchette and down to mid-perineum so that there would not be a scar where penetration would occur. This prototype surgery has influenced surgical approaches since, although scarring is no longer the operant theory of causation. A counter to this theory of causative introital scarring is the fact that millions of women sustain tears around the introitus during vaginal childbirth, and these heal with only rare sequelae of tenderness and dyspareunia. In fact, keloids, which arise from pathologic thickening of scars in ectodermal skin, never involve the vestibule, which is endodermal.

Psychological etiologies: By the early 1900s, with the new field of psychology experiencing increasing popularity, dyspareunia shifted from the category of a physical problem to being a sign of neurosis. See the "History" section below. This conceptualization meant that for much of the twentieth century, women with dyspareunia were referred to psychologists or psychiatrists for mental health therapy about

maladjustment to being sexual. Modern psychologists have refined the research on etiologic psychological factors. Studies have reported mixed findings about the prevalence of antecedent depression or sexual abuse. One study found that severe childhood physical or sexual insecurity was associated with a threefold increase in vulvovaginal pain. Sexual pain is acknowledged to be a complex cause of distress (Bergeron et al. 2015).

Irritant exposure: Many patients' first symptoms are assumed to be from a yeast vulvovaginitis, and research is ongoing to assess a relationship between candida exposure and LPV. Clinically, episodes of severe vaginitis or a reaction to over-the-counter antifungals is a feature of some women's histories of vestibulodynia. Episodes and treatments are common enough that cause and effect are hard to prove.

The use of immune modulators such as imiquimod in the fourchette/vestibule area can elevate the risk that LPV will be triggered.

8.1 Low Estrogen as a Cause of Vestibulodynia

Low estrogen levels have been found to provoke growth of genital tract nociceptive nerves in animal studies. Additionally, lower and higher estrogen levels during estrus cycles are associated with repetitive proliferation and thinning of genital nerve density, respectively. The accompanying infiltrate of T-cells and mast cells may be responsible for recognizing low estrogen levels and releasing neurogenic messengers such as angiotensin II (Brauer and Smith 2015).

The low-estrogen theory of causation holds that since vestibular tenderness is so specific to intercourse, it might be considered a strategic contraceptive condition. LPV makes intercourse intolerably painful in women who are otherwise healthy. Considering that species survival is a major rule of nature, dyspareunia during one period of reproductive life, lactation, could selectively increase survival of a newborn by postponing a next pregnancy. After high placental estrogen levels plummet with delivery, and ovarian function is suppressed during the period of lactation, low estrogen may constitute a trigger for temporary vestibular pain. Postpartum dyspareunia is common after ovarian estrogen levels fall. In a 1996 study, dyspareunia occurred in 38 % of parturients, and if it continued beyond 5 months, its resolution was specifically associated with resumption of menses (Goetsch 1999). All cases resolved by 1 year, but this provided a painful disincentive to have intercourse, thereby acting as a contraceptive by virtue of pain. Two early prevalence studies of vestibulitis (the old term for vestibulodynia) found that 25 % of patients had first noted their dyspareunia postpartum, and it had not resolved. This is a useful piece of patient history to assess.

Postmenopausal dyspareunia is also common after estrogen levels fall. Although this problem is usually attributed to vaginal atrophy, a new interpretation holds that both atrophy and vestibulodynia develop side by side, and the location of pain in patients with severe untreated vulvovaginal atrophy is the vestibule, not the vagina (Goetsch et al. 2015). A histologic study in this population has found the condition to be consistent with vestibulodynia (Leclair et al. 2013).

Figure 2 shows an example of severe vestibulodynia in postmenopause.

The theory of low-estrogen causation does not immediately seem to apply to premenopausal women, as this population has a 12–14 % prevalence of LPV despite generous levels of estrogen. The theory holds that if the introital zone is genetically primed to become tender, nonhormonal triggers may be capable of setting the neurogenic process in motion. This would explain vestibulodynia that arises after bladder infections or topical irritant use.

The theory of an estrogen trigger may also explain primary vulvar vestibulodynia (pain since first attempt at vaginal penetration in young women.) Girls have scant estrogen until puberty. Many girls may be asymptomatic but have tender vestibules, something we don't know since genital examinations are restricted in girls. Tenderness would then disappear with the rise of estrogen in puberty, only to return

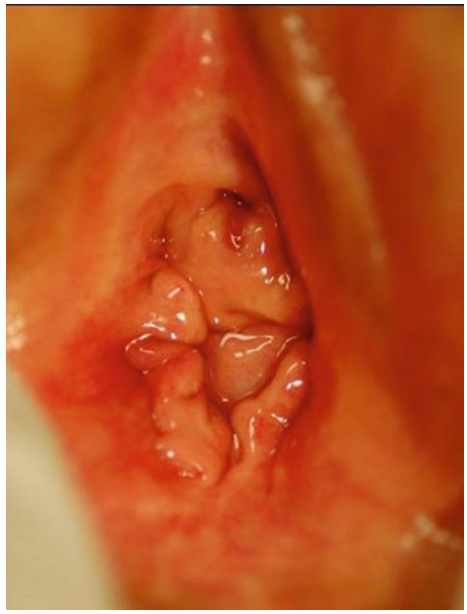

Fig 2 Severe vestibulodynia in a 64-year-old who has been without estrogen for 10 years and for whom estrogen is contraindicated due to a history of breast cancer for 3 years (Goetsch 2013)

postpartum. If, for some girls, the hormone receptor mechanism in the vestibule is faulty and the tenderness does not resolve with puberty, they are left with primary vulvar vestibulodynia despite normal estrogen levels. Primary vulvar vestibulodynia is present in 7 % of young women and may represent nature's "error" rate, so to speak.

Progesterone effect: Some researchers suggest that newer progestins with an androgenic nature be avoided.

Genetic predisposition: Data show that there are genetic variants that cluster in women with LPV, and these relate to pro-inflammatory pathways, T-cell regulators, and serotonin and androgen receptors. Findings utilizing the Utah Population Database showed shared ancestry out to seven meioses among a set of women who had undergone corrective procedures for severe LPV (Morgan et al. 2016).

Relationship to bladder pain syndromes: Not uncommonly, the clinical history in women with secondary vestibulodynia points to a bad bladder infection as a trigger. The bladder and the vulvar vestibule are both derived embryologically from the endodermal layer. A flare of symptoms in one of the two tissues can be reflected in symptoms in the other.

Triggering by human papilloma virus (HPV): Investigators initially suspected HPV to be a causative agent of secondary vestibulodynia. However, there is rarely histologic or DNA evidence of the virus at biopsy, and academic consensus is that it is not causative. Patients can give a history of pain a few months into a new relationship, however, implicating a transmissible agent. HPV may therefore be acting as a "hit and run" actor. Therapeutic approaches are not altered even if HPV seems to have been a trigger. The early popularity of interferon injections for vestibulodynia faded when efficacy was questioned.

Neuropathic pain with central mediation: Many researchers consider that both types of vulvodynia, localized and generalized, exhibit evidence of amplification of peripheral nerve impulses by intermediate synapses before they reach the brain and are perceived as pain (Zolnoun et al. 2006). Several studies have demonstrated heightened sensitivity to noxious stimuli in anatomic sites distant from the vulva in women with LPV. Whether in LPV this reflects a genetically determined variation in pain sensitivity, or a product of the peripheral LPV pain with development of central sensitization is not clear. Generalized vulvodynia is best described as a disorder with central sensitization and is most successfully treated with neuromodulators effective for peripheral neuropathy.

9 Vulvodynia's Place in the History of Medicine

Textbooks of gynecology over one hundred years ago described and offered treatments for what is now realized to be vulvar vestibulodynia and pelvic muscle hypertonus. "Vaginismus" was the original name given to this condition by Marion Sims when he presented a descriptive paper to the Obstetrical Society of London in 1861. The term "vaginismus" included both mucosal and muscle

problems. He described five patients with severe dyspareunia that prohibited coitus, noting this to be a moral issue because they had never been able to consummate holy matrimony due to their severe conditions. His term "vaginismus" would today be considered the duo of vestibulodynia with pelvic floor myalgia. He published a description of a minor surgery that revised the tissues of the introitus, and he instructed patients to follow this with the use of vaginal dilators. Over the next decades of the nineteenth century, authors of gynecologic textbooks such as Simpson, Skene, Huhner, and Kelly described this condition. When psychological diagnoses became popular in the 1880s, textbooks began introducing the consideration that women with dyspareunia were hysterical and neurotic. The description of mucosal hypersensitivity dropped out of the writings by the 1930s, and women were treated by psychologists for neuroses and by physical therapists offering dilator training. "Vaginismus" held on as a psychiatric diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM) until the newest version, 5. Before edition 5, "vaginismus" was characterized as a severe aversion to penetration without a mention of pain, noting only tight muscle spasms sufficient to obstruct penile entry. The latest DSM-5 edition has eliminated "vaginismus" in favor of "genito-pelvic pain/penetration disorder" and emphasizes the distress that it causes.

10 Comorbidities with Vulvodynia

Pelvic floor myalgia: Pelvic floor muscle tightness is usually present in LPV and can be a source of pain with penetration. Repeated, protective contractions of pelvic floor muscles can easily develop as a response to exquisite vulvar tenderness and/or deeper pelvic pain. Patients with myalgia have lost the capacity to fully relax these muscles, and there is relative weakness of the muscles despite the constant contracted state. Physical therapy is very important to help patients train these pelvic floor muscles. The American Physical Therapy Association has special certification for members who complete training in therapy to the pelvic floor. These practitioners provide expertise for issues of pelvic floor tightness and pain as well as for other problems such as pelvic relaxation and associated urinary incontinence.

Bladder issues: There are two ways that localized vulvodynia patients can develop symptoms that relate to their bladder function. In the simpler example, the increased muscle tension described above elevates the hammock of muscles thereby reducing filling capacity of the bladder and causing urinary frequency and urgency. Patients may have multiple episodes of nocturia and may complain of having a small bladder capacity. They don't have bladder pain.

As a second reason to develop bladder symptoms, there is a significant association between localized provoked vulvodynia and **interstitial cystitis**. Interstitial cystitis is a poorly understood problem of nonspecific bladder inflammation with intermittent symptoms of voiding pain, frequency, and urgency. These symptoms mimic bladder infections but patients are negative for bacteriuria. Just as occurred with vulvar pain, the terminology of bladder pain has evolved. It is now usually termed "interstitial cystitis/bladder pain syndrome." The bladder and the vestibule derive from the same embryologic layer, the endoderm. Therefore it is not uncommon to elicit a history that there is a relationship between the symptoms of the two zones. For instance, women may relate the onset of vulvar pain to a bad bladder infection. And women with both conditions may note that when the bladder condition is worse, the vestibule has a flare of pain and vice versa. Both in vestibulodynia and interstitial cystitis, 17–20 % of sufferers have both conditions. It is useful to become conversant in both conditions. A helpful measure is dietary restriction of bladder irritants such as caffeine, alcohol, citric acid foods such as cranberries, spicy foods, and artificial sweeteners. The Interstitial Cystitis Association has an informative website.

Psychosocial issues: As can be expected, sexual pain has many difficult emotional consequences for women who experience it, and it affects their partners as well. Women with sexual pain have increased levels of anxiety and

depression, catastrophizing, and lower levels of self-efficacy. Sex therapists are specialists in this area and can help with the complicated emotions and difficult communication that is so common with these pain problems. All aspects of sexuality are affected by sexual pain, including arousal and lubrication, desire, orgasmic success, and the ability to have penetration itself. Many women continue to have intercourse despite pain because the risk to their relationship seems too great if they abstain. Continued penetrative activity despite pain will likely cause and worsen pelvic floor myalgia.

Atrophy after menopause: Although for decades the problem of postmenopausal dyspareunia has been assumed to be a symptom of atrophy, recent publications have concluded that this pain condition has more in common with LPV (Kao et al. 2012) and is located in the vestibule rather than the vagina. Atrophy in other organ systems is not a cause of pain (atrophied muscles, aged skin). Specialists in menopause and vulvar pain have not aligned their concepts, but acknowledgment that neural hypertrophy is not a usual finding in atrophy will allow research to proceed regarding neurogenic vestibular inflammation of GSM that affects millions of women.

Chronic pain conditions: Vulvodynia is considered by many pain researchers to be one of several conditions that exhibit central mediation and upregulation of pain processing. Other conditions often mentioned in this list are fibromyalgia, bladder pain syndrome, irritable bowel syndrome, and migraine syndrome. One confusion about research into such groupings of pain conditions is that often no distinction is made between generalized vulvodynia, probably a centrally mediated pain process, and localized provoked vulvodynia, felt by some vulvar researchers to be a chronic but peripheral condition.

11 Therapeutic Efforts: General Points

Many therapies have been tried for vulvodynia. A criticism of most intervention studies is that they lack controls and randomization to compare therapeutic efficacy. This has resulted in a frustrating accumulation of anecdotal reports without rigorous science. Additionally, it is common that studies have failed to assign women to specific categories of generalized versus localized vulvodynia, and they have failed to group women into categories of primary versus secondary vestibulodynia. All of these factors mean that there are many answers awaiting elucidation.

Treatment of the general problem of entry dyspareunia: When this complaint has become chronic, it is usually multifactorial. The triad of factors are mucosal allodynia, secondary tightening of pelvic floor muscles, and psychic stress. Therapeutic initiatives are required for each for full treatment.

Despite acknowledgment that dyspareunia requires multimodal therapy, there is no full agreement about how to evaluate success. Researchers in the field have not established a uniform set of outcome measures. Using "dyspareunia" as an outcome, for instance, may be significant but still not be complete (i.e., intercourse is now possible but shouldn't intercourse be comfortable and enjoyable?). The IMMPACT group that has published criteria for evaluating improvement in chronic pain conditions suggests that a pain reduction of 50 % is probably of clinical significance. However, for dyspareunia, an intolerable pain that is reduced 50 % may still be unacceptable. Proportional improvement may need clarification by assessing features like the consistency of relief and the confidence associated with sexual function.

As another general point, only in menopause is estrogen therapy really helpful; pain may be ameliorated in some younger women, but the effect is not dramatic.

12 Specific Therapies for Vulvodynia

General suggestions for vulvar hygiene: Most reviews of vulvodynia emphasize reduction of local exposure to irritants, whether the irritants be sweat, soap residues in clothing, irritating body soaps or over-the-counter genital products.

Commonly used over-the-counter "intimacy" products like anti-itch or numbing benzocaine can be problematic because of skin hypersensitivity reactions and should be avoided. The use of an effective sexual lubricant is important to reduce friction across tender mucosal surfaces. Water-based lubricants are recommended when condoms are being used, but silicone lubricants can provide longer-lasting lubrication.

Multiple empiric therapies: Many pill and cream therapies have been tried empirically for all vulvodynias without scientific proof of efficacy. These include cortisone creams, hormone creams, anti-herpes therapies, antifungals, topical use of hot red pepper extract (capsaicin), and therapies used for shingles. A common impulse in response to seeing redness in the vestibule is to prescribe a course of topical steroids to the area. The inflammation of vestibulodynia, however, has been shown to be neurogenic and not a classic inflammation and is unresponsive to topical steroids. One study combined injections of steroid and anesthetic and showed efficacy in a year follow-up, but further studies were not forthcoming.

A prolonged empiric course of an oral antifungal for several weeks is standard in some approaches to vulvodynia.

Topical lidocaine therapy: For symptom relief of LPV, the most helpful therapy is topical lidocaine applied just before intercourse. Such therapy is not intuitive, as numbing a potentially erogenous area seems counterproductive. However, the numbing removes the burning allodynia and is only mucosal, so touch sensation remains. (It could be compared to the difference between a facial nerve block at the dentist's and a rinse of oral lidocaine solution.) If mucosal pain is prevented, women with this condition can learn to relax their pelvic floor muscles, thereby further reducing discomfort.

Choices of product include a gel formulation with 2 % lidocaine, an aqueous formulation with 4 % lidocaine, and an ointment with 5 % lidocaine. The benefits of the aqueous solution are its relative strength combined with a single preservative, making it less likely to sting on first application. Additionally, the liquid does not smear widely and risk numbing the partner. Patients must be shown with a mirror just where the tender zones are, and they avoid numbing the clitoris.

Pretreatment with lidocaine for several minutes immediately before intimacy, plus the use of an effective lubricant, can help many who have mild, and even severe vulvar vestibulodynia have comfortable intercourse. Clinically, premenopausal women find lidocaine use instructive to confirm the diagnosis, but unacceptable as an indefinite strategy.

Lidocaine for those who cannot use estrogen in postmenopause: Breast cancer survivors who cannot use estrogen products can get excellent results for severe dyspareunia by learning to use a compress of liquid lidocaine anesthetic applied for 3 min to the painful area (followed by lubricant) just before intimacy (Goetsch et al. 2015), Ninety-five percent of affected women in a randomized trial were able to have comfortable intercourse after preventing entry dyspareunia with lidocaine. Half of the group had been abstaining because of the severity of pain. All aspects of sexual function improved when pain was prevented, independent of the length of time the couples had had to abstain, indicating that the adage "use it or lose it" is not an appropriate exhortation. In the 2015 randomized controlled trial, postmenopausal breast cancer survivors embraced liquid lidocaine as a long-term therapy, having previously found that the prohibition against estrogen gave them no other effective therapy for severe genital pain of menopause.

Treatment of the vestibule mucosa: The most effective corrective therapy for LPV is superficial local excision of the affected mucosa (Tommola et al. 2010). More than 20 outcome series and one randomized comparative study show excision to be a successful and acceptable treatment for this condition. There has been great hesitation, however, to list this intervention as most indicated. Review publications and specialty committee reports continue to suggest that it be offered as a last resort, only after other therapies have been exhausted. Delay, however, has been shown to increase the difficulty of treating associated muscle and emotional problems. Pain for 5 or more

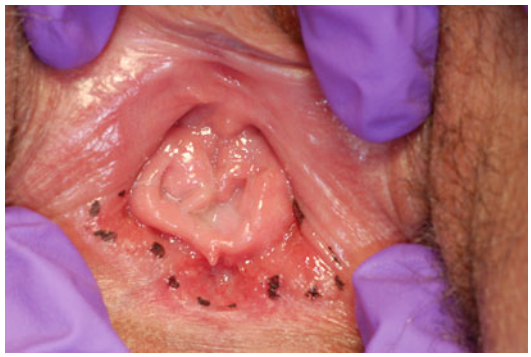

Fig. 3 This shows the mapped area of vestibulodynia before the procedure of localized mucosal removal in a patient with tenderness from 3 to 9:00. The hymen will be used as a flap to close the resected zone without advancing the vaginal tissues (Goetsch 2007)

years prior to effective mucosal therapy has been associated with a worse prognosis for cure of dyspareunia. Early diagnosis and symptom relief are important to prevent sexual comorbidities.

LPV may be a singular example of a focal unremitting inflammatory pain that is amenable to local excision. The procedures vary from uniform to individualized, the latter superficially removing only painful areas. Some techniques remove the hymen and advance vaginal wall tissue down to the perineum (vaginal advancement). Others leave the hymen and use it as a flap to close the resected zone of affected vestibule. Figure 3 shows an example prior to excision.

The extent of surgery will determine the time needed to heal and the associated disfigurement to the vulva. Techniques have not been directly compared to assess morbidity and rates of cure. Since all surgeries excise the apertures of the Bartholin's ducts and cover them with a flap, there is a risk of developing Bartholin's duct cysts at a future time, but this occurs in only 10 % of cases and may not be apparent to patients. Postoperative physical therapy and dilator use help with the relaxation of tense muscles and the transition to comfortable sex.

Another noninvasive therapy has employed the NgYag laser. It is a laser used by dermatologists for remodeling of skin collagen related to aging in nongenital areas. It is not clear what it targets in LPV, but there has been success in treating the anterior vestibule where surgical excision is not feasible by directing multiple pulses of laser energy during 1–3 treatment sessions. NgYag laser is not a destructive laser. The classic vaporizing CO_2 laser was found to have a low success rate and risked worsening the LPV; it was quickly abandoned.

Treatment of pelvic floor myalgia: Physical therapy is an important adjunct in the treatment of LPV (Bergeron et al. 2008). It addresses muscle pain (pelvic floor myalgia) and tight introital muscles that heighten penetrative friction. Physical therapy may be less important for generalized vulvodynia, as this pain condition results less often in muscle tightening. Also, generalized V often affects older women who are more likely to be multiparas with laxer muscles compared to nulliparas who constitute a significant portion of LPV patients.

The physical therapist must be specifically trained in pelvic floor muscle work. Techniques vary, and the consistent feature is to train women to recognize when muscles are tight and learn to relax them volitionally. On evaluation, muscles are usually in hypertonus but are actually weak. Biofeedback is provided either by digital monitoring by the therapist or with a vaginal sensor that assesses electromyographic (EMG) data. The goal is muscle relaxation, increased blood circulation, and enlargement of the vaginal caliber. Successful physical therapy of myalgia can reduce the degree of dyspareunia by 50 % even without addressing the vestibule tenderness. Soft or firm vaginal dilators of varying sizes can be helpful for home use so that therapy can continue for each woman independently. The ability to easily insert successive sizes of dilators confirms increasing success with relaxation. Physical therapists are a source of emotional support and patient education about anatomy and touch. Some use topical lidocaine to treat the mucosal pain of LPV in order to focus on muscle work. They can be effective teachers of home lidocaine use.

Psychosocial therapy: Sexual pain, by its nature, complicates a woman's sense of personal normalcy and sexual confidence. Professional counseling can be critical for patients and their partners, improving specific dysfunctions in

addition to the pain itself. Researchers are exploring various approaches to therapy more specific than simple supportive therapy. Cognitive behavioral therapy (CBT) has successfully focused on pain management and sexual functioning with improvements maintained at a 2.5-year follow-up (Bergeron et al. 2008). Mindfulness is being proven valuable as well, in changing perceived intensities of pain and benefiting muscle relaxation in series of group sessions. A sex counselor can be helpful by suggesting to couples a range of non-painful options for intimacy. Both parties are affected, and couples' sex therapy is important to address the shared issues of guilt, inadequacy, and shame.

Only a few studies report on therapeutic interventions that include the sexual partner.

Hormone therapies: Generalized V is not considered to be hormonally sensitive. There is not a consensus about the benefit of manipulating the hormone milieu in patients with LPV. Researchers in Sweden have concluded that one in five patients with LPV is benefited to some degree by stopping their combined oral contraceptives. Some believe that the second-generation progestin drospirenone can trigger or worsen LPV and should be discontinued. Research is ongoing about the benefit of topical estradiol/testosterone cream.

The one clear setting where estrogen therapy is definitely effective and appropriate is in menopausal dyspareunia. The therapy may need to be applied directly to the vestibule, but research lags in this area, as the general understanding of GSM assumes that the pain is from vaginal thinning. Efficacy of vaginal estrogen regimens is the subject of a Cochrane review. A synthetic estrogen receptor modulator, oral ospemifene, is available as an alternative to standard estradiol products for menopausal dyspareunia.

Diet therapy, particularly a low oxalate diet, has never been shown to have benefit in vestibulodynia. A diet restricting bladder irritants can help with bladder pain and urgency. Extreme adherence to a low oxalate diet does not provide healthy nutrition. **Neuromodulators**: Oral medicines to treat the nervous system are commonly offered by many vulvar practitioners across the country, although results vary and good comparative studies are few (Foster et al. 2010). These classes of medications include the tricyclic medicines (amitriptyline, desipramine, nortriptyline) and neuromodulators (gabapentin, pregabalin, and duloxetine).

Some of these medicines have also been mixed into a cream and applied directly to the painful vestibule (Boardman et al. 2008).

There are studies supporting the use of topical 5 % lidocaine, 2 % amitriptyline cream, and 6 % gabapentin cream as helpful for some patients. Baclofen or valium has been offered as vaginal suppositories.

Generalized vulvodynia: This disorder, characterized by aberrant nerve messaging, is not appropriately treated by surgery. Medical management is with neuromodulators.

13 Conclusion

Vulvar pain is a complicated sexual pain disorder affecting 8–15 % of all young women and at least 50 % of postmenopausal women, with even higher percentages in women who are not using supplemental estrogens after menopause such as women with a history of breast cancer. Although what we know to be vulvodynia was described in early gynecologic textbooks, it was misunderstood for decades and then "rediscovered" in the 1980s. Research is ongoing to understand the physiology and why this affects so many women. Clinicians in many specialties should be familiar with this condition and its variations in order to offer accurate diagnoses and referral for treatment. Those whose practices include genital examinations should know how to pretreat with lidocaine in order to assess upper and lower tract conditions most accurately. Therapies for vulvodynia must address not only the physical pain but the emotional and psychological distress that results. An integrated multidisciplinary approach provides the best strategy for success.

14 Cross-References

- Benign Diseases of the Vulva
- Benign Vulvar and Vaginal Pathology
- Management of Menopausal Symptoms
- Management of Pelvic Pain, Dyspareunia, and Endometriosis
- Management of Sexual Dysfunction
- Management of Vaginal and Vulvar Lesions in the Older Woman

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Management of Pelvic Pain, Dyspareunia, and Endometriosis

Judy Hall Chen

Abstract

Pelvic pain is an enigmatic diagnosis which often brings frustrations to both patient and practitioner. Within this chapter an introduction to the changing categorization of pain, a review of pain pathophysiology, and clinical approaches to three presentations of pelvic pain (general pelvic pain, dyspareunia, and endometriosis) are highlighted. Dives into the clinical approach for general pelvic pain, dyspareunia, and endometriosis stress the need for thorough interview, history documentation, and detailed physical exam findings. If these parameters fail to give a clear explanation of the etiology, other techniques may be useful to elicit other common findings associated with pelvic pain, dyspareunia, or endometriosis. Despite the trend toward algorithmic clinical practice for many disease assessments, the diversity of diagnoses related to pelvic pain limits the effectiveness of an algorithmic approach. A focus on the reproductive status of the patient impact may help to guide both diagnosis and therapeutic options.

Keywords

Pelvic pain • Dyspareunia • Endometriosis • Pain • Pain syndromes • Sensitization • Convergence • Neuronal cross-talk

Contents

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1 Introduction

Pain is the one symptom which provokes strong responses and emotions in both patients and physicians. Since the pain is often generated as a complex symptom arising out of activation of multiple levels of neural feedback loops modified by both physiologic and psychological factors, there is often difficulty in exactly isolating the exact location of the physiologic process involved in the disease. Beyond the complexity of the pain response lies the complexity of the female pelvis and reproductive system. The cyclic and systemic nature of reproductive hormones adds not only endocrine modulation of the disease process but may also affect the psychologic status of the patient. Added to this are stress factors related to fertility desire and potential. Although scientific investigation continues to unveil new understandings related to these processes, the interplay and overlap which occurs in patients with chronic pelvic pain continues to be an area that demands individual customization.

Much of this chapter focuses upon the general accepted physiology of pain perception and on areas that often cause confusion for patients and physician. The goal, ultimately, is to provide clinicians with workup and management protocols based in a firm understanding of the underlying basic pathophysiology of female pelvic pain. Although there are some innovative diagnostic tools and/or therapies that are under investigation, they often require a more in depth pursuit on behalf of the reader and thus will not be the focus of this chapter.

1.1 Terminology

Before diving into the aspects of pelvic pain related to women specifically, there is a need to outline the source of difficulty within this area: nomenclature and physiology. Prior terminology grouped much of pelvic pain into merely time constraints: less than 6 months (acute) versus more than 6 months (chronic). However, as the understanding of the different causes of pain has evolved so has the nomenclature of pelvic pain. No longer does a general diagnosis of chronic pelvic pain suffice to guide treatment. It is now important to specifying source, progression, cyclic changes and effect of medications. "Chronic pelvic pain" today as a term has evolved from merely a diagnosis to a symptom requiring further investigation and delineation.

This change in definition requires the language used to detail the symptom of chronic pelvic pain to become richer and more specific. Without modification in physician language the cognitive process of forming a differential diagnosis remains limited.

The past combination of imprecise language and static understanding of pain pathology gave rise to a frustrating cycle of generalized history taking, imprecise differential diagnosis lists, indeterminate results, and failed empiric therapy. These factors potentially give rise to a gradual split between patient and physician often leading to a change in healthcare providers with the possibility of repeating a similar experience. Repeated cycles of these events often lead to frustration and distrust on both sides of the clinical experience: patients and clinicians. Using a more precise nomenclature assists in increased diagnostic accuracy, therapeutic precision and in rebuilding patient rapport and professional communication.

Baranowski gives good scope to untangling the complexity of the current vague terminology by introducing the concept of classifying CPP into three conditions of medical understanding: phenotyping, terminology, and taxonomy (Baranowski 2009). *Phenotyping* is the process of identifying the pathophysiologic changes in order to understand the cause of the pain symptoms. *Terminology* highlights the gap between the true definition of words and the varied use of practitioners when selecting words to describe both the cause and symptoms of pelvic pain. Lastly, *taxonomy* separates *terminology* into two categories: known pathologic causes of pelvic pain versus syndromes of pain which have consistent symptom presentations but no know associated pathologic process. Expanding our understanding from a symptom, chronic pelvic

pain is now a starting point in a process to identifying diseases and syndromes as separate entities.

In 2004, the American College of gynecologists (ACOG) defined chronic pelvic pain, CPP, as noncyclical pain of at least 6 months' duration, involving the pelvis, anterior abdominal wall, lower back, and/or buttocks, serious enough to cause disability or to necessitate medical care. Similarly the World Health Organization defined CPP as constant or intermittent, cyclical or noncyclical pain that persists for 3 months or more (Latthe et al. 2006). In contrast, the European Association of Urology (EAU) and the International Association for the Study of Pain (IASP) laid aside to catch all diagnosis of "chronic pelvic pain" in favor of separating out pelvic pain with a clear attributable cause from the syndromes of pain within the pelvic area. Specifically the EAU states:

> Chronic pelvic pain is chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioral, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynecological dysfunction.
>
> *where perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) has localized the pain as being perceived in the **specified anatomical pelvic area**.

In this chapter, we will step away from older definitions of CPP and adopt the view of the EAU and IASP with the intention to give a broader systematic categorization of pelvic pain within women. Table 1 should illicit a list of the different chief complaints of pelvic pain in women.

2 Pain Physiology: Basic Concepts

Understanding the physiology of pain assists with whittling down the list of potential diagnoses. Pain as a symptom has two components. The first is concrete and has its basis within the anatomy of the nervous system. The second is more amorphous and incompletely defined and involves inflammatory protein peptides and neurotransmitters that often modify perception of pain.

The anatomy of pain begins within the peripheral nerves that contain primary afferent nociceptors and pain receptors also known as primary sensory afferents. While the largest diameter peripheral nerve fibers are the A-beta (Aβ) fibers, it is the small-diameter myelinated A-delta (Aδ) fibers and the unmyelinated axons (C) fibers which contribute the most to the detection and relay of pain signals to the central sensory cortex. These two fibers innervate skin, deep somatic structures, and visceral structures. Activation of these primary sensory afferents (pain receptors) requires the presence of a noxious stimulus or a combination of stimuli such as heat, intense mechanical pressure, or chemical irritants. Once activated these primary afferents transmit their signal to the central nervous system through the dorsal root ganglion in the spinal cord to the brain.

The integration of pelvic anatomy, inflammatory responses, and psychiatric modulation may help to obscure the primary stimulant of the symptoms as well as significant changes of symptoms over time. The changing and confusing presentation of pain symptoms occurs due to the phenomena of sensitization, convergence, and modulation.

2.1 Sensitization

Sensitization is a learning process where repeated stimuli result in a progressive amplification of a response. It is the process by which pain receptors alter the transmission of the original stimuli secondary to inflammation. Enhancing the signal transmission of the peripheral nerves are the

Table 1 European Association of Urology classification of chronic urogenital pain syndromes (Reprinted with permission Fall et al. 2009)

Axis I region		Axis II system	Axis III end organ as pain syndrome as identified from Hx, Ex, and Ix		Axis IV referral characteristics	Axis V temporal characteristics	Axis VI character	Axis VII associated symptoms	Axis III psychological symptoms
Chronic pelvic pain	pelvic pain syndrome	Urologic	Bladder pain syndrome Urethral pain syndrome Prostate pain syndrome Scrotal pain syndrome Penile pain syndrome Endometriosis associated pain syndrome	(See Table 5 on ESSIC classification) Type A inflammatory Type B noninflammatory Testicular pain syndrome Epididymal pain syndrome Post-vasectomy pain syndrome	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks	Onset Acute Chronic Ongoing Sporadic Cyclical Continuous Time Filling Emptying Immediate post Late post	Aching Burning Stabbing Electric Other	Urinary Frequency Nocturia Hesitance Poor flow Pis en deux Urge Urgency Incontinence Other Gynecological e.g., Menstrual	Anxiety About pain or putative cause of pain Other Depression Attributed to pain/ impact of pain Attributed to other causes or unattributed Shame, Guilt related to disclosed or undisclosed sexual experience/s PTSD symptoms Reexperiencing Avoidance Hyperarousal
		Gynaecologic	Vaginal pain syndrome Vulvar pain syndrome	Generalized vulvar pain syndrome Localized vulvar pain syndrome	Vestibular pain syndrome Clitoral pain syndrome	Provoked		Sexual e.g., Female dyspareunia impotence Gastrointestinal *** Muscular Hyperalgesia	Monosymptomatic delusions
		Anorectal							
		Neurologic	e.g., Pudendal pain syndrome					Cutaneous Allodynia	
		Muscular							
	Nonpelvic pain syndromes	e.g., Neurologic e.g., Urologic	e.g., Pudendal neuralgia						

Hx history, *Ex* examination, *Ix* investigation, *ESSIC* European Society for the Study of IC/PBS, *PTSD* posttraumatic stress disorder

inflammatory markers produced during tissue injury including bradykinin, prostaglandins, and leukotrienes. The threshold for activating the afferent nociceptors and pain receptors is lessened and the frequency of firing is increased when intense, repeated, or prolonged stimuli are applied to damaged or inflamed tissue. This may result in innocuous stimuli to become noxious (Fields and Martin 2001).

Sensitization can be triggered in an autocrine fashion via the pain receptor itself. Once triggered, pain receptors produce inflammatory factors which then can alter the original response. Sensitization contributes to the sensation of tenderness, soreness, and hyperalgesia. Frequently, the repetitive occurrence of tissue injury can further shape the response of pain receptors to cause a new response not previously associated with such stimulation. This process causes an evolution of neuronal response to persistent stimulation (Jones 2001).

Primary afferent nociceptors may also activate an autocrine response through the production of substance P, a neuropeptide unique to neuronal tissue. Substance P impacts the transmission of pain signals by increasing vasodilation, degranulation of mast cells, release of leukocytes, and even production of inflammatory markers. This multimodal process increases sensitivity of pain signaling and interpretation and may contribute to evolving pain complaints and triggers.

2.2 Convergence

There are several theories describing the mechanisms behind referred pain. Convergence is where multiple primary afferent axons connect with multiple different central spinal neurons (the dorsal root ganglion) that in turn may also contact multiple different afferent axons. This "mixing" of transmitters and receptors within the nervous system leads to the phenomenon known as referred pain. The most common example of referred pain is the irritation of the diaphragm being perceived as shoulder pain. While each dorsal root ganglion is associated with a dermatomal section for skin innervation, it also receives **signals from internal organs and/or deeper musculoskeletal structures.**

While sensitization can modulate an individual's response to an activated pain receptor, convergence can obscure the origin of the pain receptor.

Convergence and sensitization within the pelvis have also been referred to as "neuronal cross talk," where the activation of the neuronal system by one organ system within the pelvis alters the threshold as well as response of another organ system (Pezzone et al. 2005). Both the overlapping nature of the autonomic sacral plexus and the inflammatory markers of the paracrine system function to produce a "neuronal cross talk" within the pelvis. This cross talk effectively functions both as a modulator of primary afferents to all the pain receptors within the pelvis and also as unique triggers in themselves.

2.3 Modulation

Pain modulation is an increase or decrease in the sensation of pain due to outside stimuli. The "Gate Control" theory postulates that nonpainful input "closes the gates" to painful stimuli, thus blocking pain sensation from reaching the CNS. The "Gate Control" theory or the "Gate Theory" has led to development of transcutaneous electrical nerve stimulation (TENS) for pain relief. There is also the well-known phenomena called "stress induced analgesia" linked to situations on the battlefield or arena where wounded soldiers or injured athletes report that they feel no pain. Pain information heading to the CNS may be modulated by ascending and descending inhibitory systems through endogenous opioids, endogenous serotonin, spinal cord inhibition, peripheral nerve stimulation, or exogenous analgesics.

There is a complex response to pain stimuli that varies greatly from subject to subject. The perceived pain sensation is often heavily influenced by the emotional state.

Neural pathways that are often associated with modulation of chronic pelvic pain are those associated with mood and emotion. Mood and emotions can strongly modulate how pain is perceived.

> In healthy volunteers, positive affect was associated with reduced pain, while negative mood was associated with amplification of pain sensations (Meagher et al. 2001). Psychiatric disorders have a good correlation with increased pain symptoms with depression occurring as a comorbidity about 30-40% of the time (Holdcroft and Jaggar 2005).

The exact molecular mechanisms in which psychiatric disorders modulate pain perception have yet to be delineated. However, evidence indicates that psychological variables such as expectation and anticipation influence "pain-modulating circuits" between the brain and pain-transmission pathways. One such "pain-modulating circuit" links the hypothalamus, midbrain, and medulla with the spinothalamic and spinoreticulothalamic pathways (Jones 2001). In this circuit, the opioid receptors are responsible for both inhibiting pain responses as well as enhancing pain responses. This is possibly one of many contributors to the phenomenon of opioid-induced hyperalgesia (Jones 2001).

2.4 Neuropathic Pain and Nociceptors

Direct damage to the somatosensory nervous system may result in a type of pain called neuropathic pain. Neuropathic pain may include dysesthesia (abnormal sensations) or allodynia (normally non-painful stimuli). Common qualities of neuropathic pain include burning or coldness, "pins and needles" sensations, tingling, numbness, and itching. In addition to nerve damage, however, these sensations can also be triggered by strong nociceptive stimulation (Berkley 2005). Nociceptors are nerve endings that are found in the high numbers in the skin, but also on internal surfaces as the periosteum, joint surfaces, and some internal organs. They are stimulated by damaging mechanical, thermal, and chemical stimuli. The differentiation between the two sources of neuropathic pain [direct nerve damage or activation of nociceptors] currently requires direct testing of nerve conduction of the specific nerve in question. This becomes difficult when the specific nerve in question lies with a visceral organ and as is often the case, within the pelvis.

Assessing neuropathic pain relies upon detailed, careful descriptions of pain complaints and the clinician may find useful available pain scales. The Leeds assessment of neuropathic symptoms and signs scale (LANSS) may assist with teasing out the elements of history that increase the likelihood that there is true tissue damage. However, a clear separation of the overlap between the effects of persistently stimulated nociceptors versus true neuronal damage is sometimes very difficult.

2.5 Understanding Pain Physiology: Summary

Overall, an understanding how sensitization, convergence, modulation, and neuropathic pain influence pain acuity and chronicity plays a vital role in guiding clinical evaluation. Accurate and detailed descriptions of pain symptoms, intensity, duration, site, modulating factors, type of pain, and response to medication coupled with a documentation of the changes in these parameters over time provide an optimal base for accurate evaluation. The process of sensitization and neuroplasticity (changes in the brain throughout a person's life) may cause confusing and changing patterns of complaints. Perceiving pain as a syndrome, which allows for evolution of a neuroplastic response, rather than an isolated injury process assists in both the process of patient education as well as treatment selection.

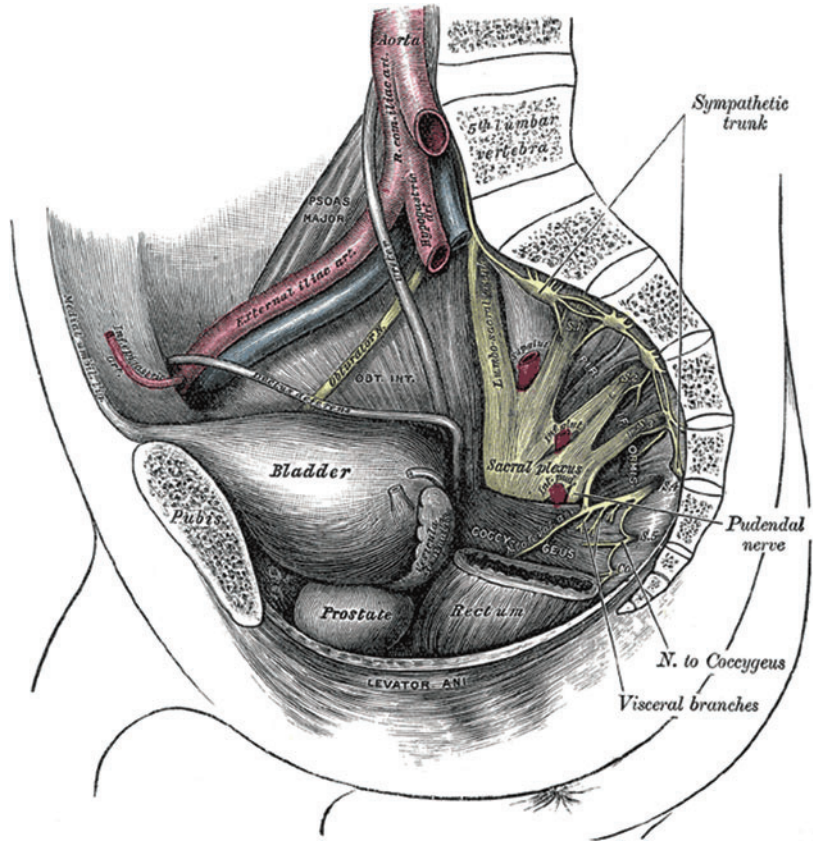

Fig. 1 Female pelvis with relation of major organs (Gray's anatomy. 1918, www.bartleby.com/107/, plate 829)

3 Pelvic Pain Management

Now armed with an understanding of the physiologic pain response at the neuronal level, the clinician can better evaluate and manage female pelvic pain. Consistent with the overlapping of the neuronal response of pain, the female pelvis has multiple levels of overlap between organs, innervation, and hormonal cycling. The complexity of the anatomic structures and their neuronal innervation in the female pelvis coupled with the impact of hormonal changes plays a central role in many common pelvic pain syndromes in women including dyspareunia and endometriosis.

Complaints of pain within the female pelvic region are common. The prevalence of chronic pelvic pain worldwide has been estimated to be about 16–82% for dysmenorrhea, 8–21% for dyspareunia, and 2–24% for noncyclical pain (Latthe et al. 2006). The wide range of prevalence speaks to the difficulties of consistent diagnostic criteria and the underlying complexities affecting pain symptoms (Berkley 2005; Winnard et al. 2006). Within the pelvis, pain stimuli may arise from any of the following: the bony pelvis, the musculature of pelvic floor and abdominal wall, vasculature, nerves, reproductive organs, bowel, ureter, and bladder (see Fig. 1).

> Rat models have demonstrated both mechanical as well as chemical "sensitization" of the urinary tract in response to colonic irritation. The frequency of bladder contractions increased and threshold of firing decreased when exposed to inflammatory markers (Ustinova et al. 2006). Studies highlight how pain perceptions may inaccurately point to the true physiologic process that is occurring at the visceral level.
>
> In other words, disease within one pelvic organ system may be the source of afferent nociception in a separate pelvic organ thus the pain perceived.

Confounding the complexity of both the pelvic anatomy and neurophysiology, female patients

have an added modulator of pain, the influence and fluctuation of reproductive hormones.

> Dr. Berkley and her team demonstrated in a rat model that the spread of inflammatory markers to the colon, uterus, bladder fluctuated with the cycling of progesterone (Winnard et al. 2006). Particularly, they demonstrated that cross-organ interaction increased during the proestrus stage (presence of progesterone), lending evidence to the difference between pain descriptions of women and of men – particularly the cyclic nature of pain.

While these studies do not delineate the entire physiologic process behind cyclic pain, it does offer insight into the factors influencing how pain changes in women. Integrating an understanding of fluctuating inflammatory markers secondary to reproductive hormones into the concept of "neuronal cross talk" adds insight to the confusing and often changing pattern of chronic pelvic pain in cycling women.

Since female pelvic pain may vary within ovulatory cycles, the clinician should consider closely the changes of complaints during the menstrual cycle. Establishing the status of patients as premenarchal, peri-menarcheal, reproductive age ovulatory, reproductive age nonovulatory, perimenopausal, and postmenopausal is important. As patients progress through stages of their reproductive status, their pain will likely change and require different treatment plans. The causes of pain in the menarcheal teenager not only differ from the postmenopausal woman but often differ from their closer peers in the early reproductive years. Thus, determining the ovulatory status of a patient should impact not only patients with complaints of infertility but also patients with pelvic pain.

3.1 Pelvic Pain Story

Of primary importance to the clinician is an understanding of the "story" each patient with pelvic pain tells. Particularly at the first visit.

In no other diagnostic process (with possibly the exception of a psychiatric history) is the history intake so vitally essential and pivotal. Many patients with pelvic pain have been seen multiple times by healthcare providers and tell stories of multiple diagnosis and treatment failures. They often bring with them not only the physiologic pain issue but also the emotional complexity related to a cycles of hope and failure. A primary key in caring for patients with pelvic pain is patience, particularly during the first visit. At his time the opportunity to build trust and cooperation with the patient becomes the cornerstone for all subsequent interactions. From this point on, the ability to negotiate a patient alliance in the process of investigation and therapeutic trials has often been set.

The complex nature of the neuronal response, pelvic anatomy, and female hormonal status does not lend itself to quick and clear diagnoses within a few visits. Rather these complexities require the clinician and patient to commit to a long-term cooperative relationship.

Chronic pelvic pain should be viewed in the same manner as that of other chronic morbidities like hypertension or diabetes.

This view of chronic pelvic pain when established at the initial visit not only manages patient expectations but also physician expectations as the patient evolves through a cycle of success and failure under their care.

Given the dual nature of pain as both a physiologic reaction and a psychiatric response, the goal of the first interview should be to first understand the contributing physiologic factors as well as the psychologic factors before determining the needed diagnostic exams or therapeutic interventions. Frequently the best care models for these patients are ones which approach the management of pelvic pain from a team perspective. Depending upon the resources available to a clinic, the medical team should not only include the primary physician and nurse evaluating the patient but also extend to other physician specialists, physical therapists, and mental health support (Chaitow

and Jones 2012). Novel models may even extend the mental health support team to include social service support depending upon the nonmedical needs of the patient.

During the initial visit, the history of present illness (HPI) should have three sections of focus: the classical description of the nature of the pain, the time course or evolution of the pain, and finally the history of the different assessments and prior treatments. Sufficient inquiry should be made to maximize the clinician's understanding of the patient's perception related to each of the above three areas. It is particularly helpful to note the emotional response of the patient as they describe each component in detail. The emotional response becomes an indicator as to severity of each symptom and the overall impact on her life style.

> The classical process of investigating the "**seven attributes of a symptom**" has no greater relevance than with pain. Detailing the location, quality, severity, timing, remitting/exacerbating factors, associated manifestations, and environmental influences of the patient's pain complaints is critical (Bickley and Szilagyi 2012).

Pointed questions to specific known events (either physiologic – i.e., ovulation – or psychologic – i.e., a loss of a loved one) and any change in the "seven attributes" of the pain will lead to improved differentiation between the three influences of pain (primary source, pain physiology, hormonal). Lastly, documenting results of past medical treatments adds information as to the primary source of the original injury, the influences of hormonal changes, and the possible presence of multiple diagnoses.

The patient's medical history becomes the second most influence portion in the initial interview. While this portion of history taking may appear routine and basic, the additional information obtained clarifies current diagnoses and may expand investigational and treatment options. Specific medical problems that may modulate pain responses include diabetes, rheumatologic diseases, inflammatory diseases, or prior surgeries. Reviewing medication history is also important and may add information such as highlighting pain modulation and behavior related to current or past medications.

Importantly for female patients, a thorough gynecologic history cannot be avoided. The elements of the last menstrual period, menarche, dysmenorrhea [now and in past], number of pregnancies, types of deliveries or terminations, delivery complications, regularity of cycle length, bleeding duration, flow of bleeding, prior sexual infection exposure and treatment courses, and current and past contraceptive usage. An additional element of the gynecologic history requires a review of pap smear screening. While it usually does not directly add insight into the patient's pain history, it may provide further information of the patient's awareness of their own health status and needs. Lastly, it is worthwhile to spend some time understanding the patient's psychiatric history.

Finally, the last element is a complete and careful physical and pelvic exam. Specific recommendations are as follows:

1. Go slow. This cannot be stressed enough. Much of the "pain" reaction of patients during this exam is provoked by clinicians who perform this exam without much warning and with extreme rapidity or roughness.
2. Limit the amount of palpation to directive, purposeful movements.
   a. Directive palpation of the external genitalia, vaginal entrance (hymenal ring), vaginal walls (anterior, posterior, lateral), levator ani muscles, cervix, uterus, and adnexa may help to identify a precise area of provocation.
   b. Usage of a single digit or q-tip may help to further elicit a precise pain response and thus a specific diagnosis.
   c. Bimanual assessment of uterus should focus on assessment of size, mobility, and position within the pelvic cavity. Cervical motion tenderness is noted. Ovarian assessment is primarily focused upon the presence or absence of fullness from a mass, not on the presence or absence of normal ovaries.

d. Rectovaginal assessment allows for assessment of abnormal tissue growth (whether a mass or disease invasion), mobility of organs in contrast to bony pelvis, tenderness, and cul-de-sac disease.

3. Speculum assessment requires the proper size speculum
   a. Standard metal speculums have a Grave's speculum design which has a wider nose and thus more useful in parous women.
   b. Standard plastic speculums have a Peterson's design which has a narrow nose and thus more useful in patients with narrow or tight introituses.

3.2 Confirming Suspicion with Objective Data

> The approaches to lab work and radiologic investigation mirror two philosophies within medicine: investigate based upon ordered differential diagnosis list and investigate based upon anticipated "worst" outcome priority.

Frequently blood work will include a complete blood count and a comprehensive metabolic panel. Additional laboratories include inflammatory markers, sedimentation rate or (hs)CRP or Ca-125 when endometriosis is suspected. Rheumatologic disease screening is particularly good in patients with systemic pain complaints. A pelvic ultrasound confirms findings of enlarged pelvic organs or masses found on physical exam or on ovarian masses or tubal pathology. It is also the best imaging option to delineate the pelvic organs as it offers the least amount of radiation exposure. The role of a CT scan or a MRI in the setting of chronic pelvic pain is to assist with diagnosis and surgical planning or to rule out suspected or unsuspected malignancy.

3.3 Management and Treatment Options

- Risk factors for endometriosis include heavy monthly menstrual flow, menstrual outflow obstruction, and family history. Common symptoms include cyclic pelvic, lower back or rectal pain, severe menstrual cramps, deep dysmenorrhea, painful bowel movement, and primary infertility. The Ca-125 is often elevated. Pelvic ultrasound or MRI may show an endometrioma if present but will not show endometrial implants. Laparoscopic confirmation of endometriosis is rarely recommended as the first line treatments are Mirena IUD, progestin dominant oral contraceptive pills, and cyclic NSADs. Second line treatments include gonadotropin agonists and contraceptive implants. [see below]
- Dyspareunia on entry and/or deep penetration can be due vulvovaginitis, STDs, herpetic lesion, injury to vulva or vagina, atrophic vaginitis, vaginal inlet obstruction, vaginismus, lichens sclerosis, or vulvodynia [chronic pain affecting the vulva]. Dyspareunia on deep penetration may be caused by uterine fibroid or mass, pelvic endometriosis, ovarian cyst, ectopic pregnancy, pelvic adhesions. Evaluation of vulva or vaginal discharge, redness, injury, lesion, pregnancy test, ultrasound findings, menopausal status along with detailed description of the complaint generally leads to the correct treatment option. [See below] (Table 2)
- Systemic complaints, complaints that present across multiple organ systems, require a thorough investigation of diseases which present in a systemic fashion (i.e., rheumatologic pathologies, immunologic pathologies). Treatments targeting only the pain will palliate but not treat many systemic disease presentations.
- Musculoskeletal complaints of the pelvic floor (ranging from spasms of vulvovaginal area to dyspareunia to incontinence) require a systematic and detailed physical exam. Through the combination of a thorough history and precise pelvic exam one can often consult with a physical therapist with a specialty in pelvic floor

Table 2 Factors associated with either deep or superficial dyspareunia (Reprinted with permission, Meana and Binik 2011). [a]inconsistently associated with deep dyspareunia

Conditions[a] associated with deep dyspareunia	Conditions associated with superficial dyspareunia
Lack of arousal necessary for vaginal lengthening or lubrication	Vestibulodynia
Chronic cervicitis	Vulvovaginitis
Repeated cervical trauma	Sexually transmitted infections
Bowel disorders (i.e., IBS)	Vulvodynia
Endometriosis	Vaginismus
Ectopic pregnancy	Vulvar dermatoses
Vulvovaginitis	Congenital anomalies
Pelvic adhesions (secondary to infection or surgery)	Obstetrical sequelae (i.e., episiotomy scars)
Uterine fibroids	Bowel disorders (i.e., IBS)
Pelvic inflammatory disease	Vulvovaginal atrophy
Pelvic congestion	Neurologic disorders
Pelvic organ prolapse	Muscular abnormalities (i.e., pelvic floor hyper- or hypotonicity
Urologic disorders (i.e., painful bladder syndromes)	Neoplastic vulvar lesions
Fibroids, pelvic mass, ovarian neoplasm, cyst	Urologic disorders

function to develop a treatment plan which have durable efficacy. Surgical corrections are available in some instances. Use of NSAIDs can also be effective.

- Myofascial trigger points have been associated with increased sensitization and cross-activation of other pain syndromes within the pelvis – particularly those related to urinary complaints, sexual dysfunction, and vulvovaginal pain (Chaitow 2007). Deactivation of these sites often impacted the pain perceived from the above related sites. Manual deactivation lies within the realm of the rehabilitation therapist; however, clinicians may also rely upon trigger point injections at sites of extreme tenderness.
- Bulk symptoms (ranging from pressure to increasing abdominal girth) should also include a thorough investigation of associated gastrointestinal complaints, radiologic investigations, as well as consideration of a risk profile for carcinoma. Ultimately, treatment may involve surgical excision and a referral to a gynecologic surgeon.
- Perimenopausal complaints require an understanding of the perimenopausal period. Perimenopause is defined as the 4–5 years before the onset of menopause punctuated by symptoms of hormonal fluctuations: irregular cycles, hot flashes, vaginal dryness, dyspareunia headaches, mood and sleep disturbances. As previously mentioned, the process of sensitization is modulated by the cyclic nature of estrogen and progesterone, thus any changes to this cycling may modify pain sensation. Low dose hormonal replacement often has efficacy.
- Mental health and mood disorders can modify the perception of the severity of their disease. Descriptions of pain symptoms which appear out of proportion of believed triggers; persistent pain which does not fit a generalizable physiologic pattern may require inquiries into the state of the patient's mental health. Again, having a therapeutic team available to assess these patients not only provides comprehensive care for difficult diagnoses and assists in managing efficiencies within the medical system.
- Neuropathic pain as mentioned previously may not be easily identified as true neuronal damage versus persistent stimulation of the neuronal tissue, but idiopathic modulation of the neuronal tissue can be done through the usage of both tricyclic antidepressants and neuromodulators such as gabapentin. Such

usage may not elicit the true pathophysiology, and a thorough work up of the pain should be pursued. Consultations with physical therapy and neurology may enhance the therapeutic process.

- All facets of the inflammatory processes can be applied to basic nociceptive triggers and often are difficult in isolating the original source of the inflammation. Thus, not all NSAIDs are effective and not all antibiotics treat pelvic pain.
- Given the potential severity of pelvic inflammatory disease it is always reasonable to treat for suspected PID, first, but close follow-up should be practiced to elicit any changes or persistence of pain which will require further investigation into the proper diagnosis.

3.4 Dyspareunia

Dyspareunia is considered a part of the spectrum of female sexual dysfunction though generally is described as pain with intercourse. It spans the spectrum of pain during any portion of the sexual response cycle. The *International Classification of Disease* 10th revision attempts to attribute dyspareunia to either organic or nonorganic causes, and the *Diagnostic and Statistical Manual of Mental Disorders* 4th revision separates the origin of dyspareunia into psychologic factors versus combined factors (Meana and Binik 2011). While the terminology and the complexity of neuron physiology plague both chronic pelvic pain and dyspareunia, other factors such as culture, personal opinions of morality and ethics, and societal perceptions influence the patient-physician interaction and subsequently clinical investigation and treatment further complicate the process of diagnosis and treatment in patients with complaints of dyspareunia.

As women continue to delay reproductive activity but maintain an active sexual life, questions surrounding sexual activity and capacity have become more common place. The World Health Organization in 2006 estimated that about 8–22% of sexually active female reporting painful intercourse with 26% attributing their sexual difficulties to dyspareunia (Meana and Binik 2011). The variety in the reported prevalence of dyspareunia arises from differing definitions used to define dyspareunia and characteristics of the target study group: age, educational level, socioeconomic standing, and comorbid conditions, particularly urinary complaints (Palacios et al. 2009). Estimates of dyspareunia prevalence increase when the study population is composed of "high risk" populations such as chronic pelvic pain patients or patients with reported female sexual dysfunction.

In contrast to chronic pelvic pain, well-defined approaches to history taking, physical exam, and diagnostic investigation have not been a part of the educational standard within women's health. While scientific literature and experts within the field exist, clinicians continue to struggle with caring for women with sexual complaints. As dealing with chronic pelvic pain, patients with dyspareunia require clinicians to understand the overlap and integration between pathology and psychological symptoms. The DSM IV defines dyspareunia as recurrent or persistent genital pain associated with sexual intercourse which causes personal distress (Mimoun and Wylie 2009). In approaching patients with these complaints, often the first hurdle is managing the patient's distress surrounding her pain.

3.5 The Sexual Stages and Categories of Sexual Dysfunction

Beginning with the stages of the sexual response cycle in women, two models have been described. Masters and Johnson described a cycle of four stages: stimulation leads to excitement – plateau – orgasm – resolution. Kaplan describes the sexual cycle as stages of desire, arousal, orgasm, and resolution. In contrast, Basson adds a layer of complexity by acknowledging the psychosocial aspects and influences of emotional intimacy (Clayton and Hamilton 2010). Satisfaction in an individual's sexual response does not depend upon the completion of all these aspects. A lack

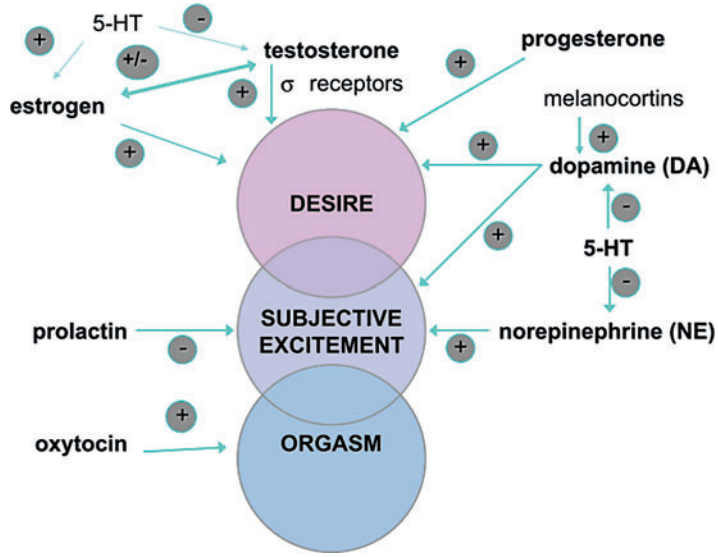

Fig. 2 Central effects on sexual function. + indicates a positive effect; − indicates a negative effect (Reprinted with permission Clayton and Hamilton 2010)

in any of these four areas may cause disruption in a patient's sexual satisfaction.

The 2017 ICD-10-CM R37 clinical describes sexual dysfunction, unspecified as "a change in sexual function that is viewed as unsatisfying, unrewarding, inadequate or deleterious." This category is further divided into multiple specific causes. In the largest and most diverse cross-sectional studies on menopausal women in the United States, SWAN (Study of Women's health Across the Nation) describes six variables related to sexual outcomes in menopausal women (Avis and Green 2011): Importance of sex, sexual desire, frequency of activities and physical pleasure (both intercourse and masturbation), emotional satisfaction with partner, arousal, and pain. The diagnostic criteria of *sexual dysfunction* used by the DSM IV-TR is divided into multiple categories including sexual desire disorders, sexual arousal disorders, and orgasmic disorders sexual pain disorders. The categories and criteria of sexual pain disorders are listed below.

DSM IV-TR: Sexual pain disorders are divided into two sections.

- Dyspareunia
  - Recurrent or persistent genital pain associated with sexual intercourse **causing marked distress of interpersonal difficulty.**
- Vaginismus
  - Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal intercourse **causing marked distress or interpersonal difficulty.**

A discussion between clinician and patient regarding the level of distress is important. A conversation defining the goals of sexual function may have more impact than anticipated within the context of managing dyspareunia.

Hormonally, current understanding has defined roles for both sex hormones and neurotransmitters within the stages of sexual desire/excitement and sexual arousal (Fig. 2). While specific female hormone–receptor combinations and cellular cascades have not been fully delineated, all the sexual hormones (testosterone, estrogen, progesterone) play a part in increasing sexual desire and maintaining organs during arousal (Fig. 3). How each hormone interacts with the other and in which manner continues to be an area of study. While no direct association has been made

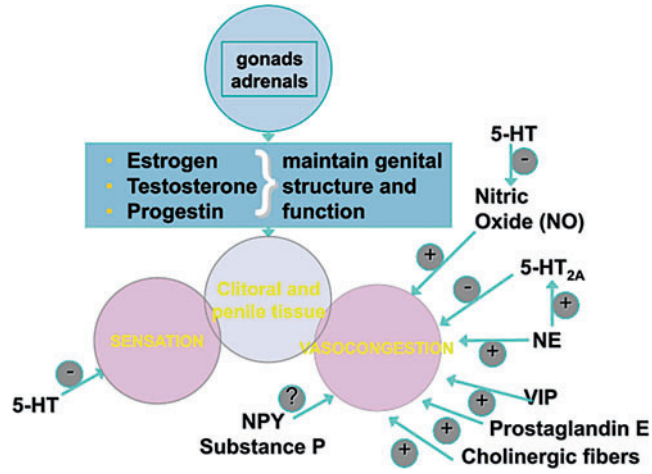

Fig. 3 Peripheral effects on sexual function. + indicates a positive effect; − indicates a negative effect (Reprinted with permission Clayton and Hamilton 2010)

between changing levels of estrogen and decreasing sexual outcomes, there does appear to be an association between increasing vaginal dryness and increasing complaints of dyspareunia. Dyspareunia can occur during the early stages of the perimenopausal period or late stages. Studies show effectiveness of vaginal or systemic estrogen replacement with decreasing dyspareunia.

> Animal studies demonstrate a role for dopamine in the stimulation of sexual desire, arousal, and drive (Hull et al. 1993). In drilling down to individual stages of the sexual cycle, norepinephrine is known to play a role in arousal while oxytocin is known to play a role in orgasms.

3.6 Management of Dyspareunia

With complaints of dyspareunia there is a need to differentiate between the two biggest categories of pain with intercourse: dyspareunia versus vestibulodynia. More general terminology divides dyspareunia into deep dyspareunia and superficial dyspareunia (Meana and Binik 2011). Often deep dyspareunia is associated with pathology deeper within the vaginal canal, cervix, and pelvic cavity. Superficial dyspareunia is associated more with the external genitalia and vaginal entrance (hymen). Meana et al. describe a list of factors associated with either deep or superficial dyspareunia in their publication on chronic pelvic pain (Table 2) (Meana and Binik 2011).

While the factors related to superficial dyspareunia tend to be more consistent in their presentation, the exam associated with delineating between deep and superficial is more detailed and extensive than a routine pelvic exam. Examining these patients requires a pre-exam suspicion leading to a detailed exam of the external genitalia occasionally utilizing a q-tip or finger for localization of pain responses along individual portions of the external genitalia. The portions of the external genitalia examined include mons pubis, labia majora, labia minora, clitoral hood, urethra, skene's glands, hymen, bartholin's glands, introitus, and vulva. Special attention should be given to the specific areas of complaint by the patient.

Evidence of infection, lesions, erythema, swelling, color changes, and differential texture should also be noted. As the exam progresses to the vaginal canal, usage of a single digit at the beginning of the bimanual portion of the pelvic exam is recommended. The bimanual exam includes a directive palpation of the vaginal canal along the anterior, lateral, and posterior walls in a sequential manner. Palpation of the cervix should be done in a manner to isolate the cervix from the vaginal walls thus decreasing any confounding response from vaginal tenderness. Assessment of the uterus and adnexa should proceed noting any masses and/or tenderness. Attention is paid to abdominal findings of guarding or distention. Often the smallest Peterson billed

Table 3 Therapeutic options for the listed conditions contributing to complaints of superficial dyspareunia

Conditions associated with superficial dyspareunia	Therapeutic options
Vestibulodynia	Lidocaine gel prior to intercourse, capsaicin cream, anti-tricyclics (either oral or vaginal), severe symptoms may benefit from trigger point injections, as a last resort – surgery may be indicated
Cyclical vulvovaginitis	Suppression of cause of vulvovaginitis if infective versus steroidal creams for systemic inflammatory complaints
Sexually transmitted infections	Appropriate antibiotic/parasitic treatment
Vulvar dermatoses	Therapy should target pathology results
Congenital anomalies	Depending upon diagnosis: surgical intervention, vaginal dilators, hormonal therapy, etc.
Obstetrical sequelae (i.e., episiotomy scars)	Vaginal dilators versus surgical intervention
Vulvovaginal atrophy	Vaginal estradiol preparations versus Premarin®, systemic hormone replacement
Neurologic disorders	Consultation with neurologist for systemic manifestations is recommended
Muscular abnormalities (i.e., pelvic floor hyper- or hypotonicity	Vaginal dilators, muscle relaxants via a vaginal route, relaxation techniques, pelvic floor physiotherapy, antidepressants versus antipsychotics
Neoplastic vulvar lesions	Treatment according to pathologic diagnosis
Urologic disorders	Kegels, pelvic floor physiotherapy, vaginal estrogen may consider comanagement with a urogynecologist depending on the diagnosis
Bowel disorders	Treatment for constipation, consideration of comanagement with a gastroenterologist depending upon diagnosis

speculum is better tolerated than a typical Graves speculum. One should not shy from frequent exams as they may be necessary to narrow down the differential as complaints persist or alter.

During this pelvic exam, attention should be paid to any area of chronic skin changes or abnormal growths within the vagina or cervix which necessitates a biopsy for complete assessment. Cultures for sexually transmitted infections or wet mount can be performed to help differentiate possible infectious contributors to the complaints of dyspareunia. Vaginal smears can be used to assess for atrophy. Other laboratory investigations vary based on suspected systemic disease (such as diabetes). Radiologic investigations starting with pelvic ultrasound may be useful to confirm physical exam findings during the bimanual exam but are not mandatory in the process of evaluating dyspareunia.

Treatment should be targeted as suspicion for particular diagnoses arises whether for an infection, neoplasm, atrophy, etc. In Table 3 is a list of therapeutic options for the listed conditions contributing to complaints of superficial dyspareunia.

Conditions and therapeutic options associated with deep dyspareunia are shown in (Table 4).

3.7 Endometriosis

The incidence of endometriosis in premenopausal patients with chronic pelvic pain symptoms ranges from 35 to 50%, while the overall incidence in all women is about 10% (Burney and Giudice 2012). The two complaints most often associated with the presentation of endometriosis in premenopausal reproductive aged women are pelvic pain or infertility. It is suggested that about 20–50% of patients with infertility have endometriosis and that about 30–50% of patients with endometriosis have infertility (The Practice Committee of the American Society for Reproductive Medicine 2006). In a comparison to fertile women, infertile women have up to a 6-to 8-fold increased risk for endometriosis. Given the variable pain presentation of patients with endometriosis, a complaint of infertility triggers considerations of endometriosis. When the chief

Table 4 Treatment options for deep dyspareunia complaints

Conditions* associated with deep dyspareunia	Therapeutic options
Lack of arousal necessary for vaginal lengthening	Counseling, self-experimentation with arousal techniques, vaginal dilators, vibrators
Chronic cervicitis	Treatment as dictated by the CDC
Repeated cervical trauma	Surgical options for excision
Pelvic endometriosis	Hormonal suppression (oral vs. injection), surgical excision
Pelvic adhesions (secondary to infection or surgery)	Appropriate treatment if infective, surgical excision
Uterine fibroids	Medical therapy to decrease size, surgical excision, ultrasonic options in certain institutions
Pelvic inflammatory disease	Treatment as dictated by the CDC, interventional drainage if abscess is present, surgical excision
Pelvic congestion	Hormonal suppression, surgical excision
Pelvic organ prolapse	Kegels, pessary, surgical excision with repair
Urologic disorders (i.e., painful bladder syndromes)	Kegels, targeted medical therapy depending upon diagnosis, pelvic physiotherapy, surgical interventions per urogynecologic recommendations
Bowel disorders (i.e., IBS)	Treatment targeting constipation, consultation of a gasteroenterologist

*Inconsistently associated with deep dyspareunia

complaint of a patient is infertility, the clinical investigation process must expand to include the appropriate overall infertility testing.

Despite the high incidence of endometriosis among symptomatic patients in their reproductive life, an average 6.7 years often pass before a diagnosis of endometriosis is determined (Nnoaham et al. 2011). Evaluation of ovaries by transvaginal ultrasound is often first line treatment for patients presenting with ultrasound especially when complaints on dysmenorrhea or dyspareunia or pelvic pain.

3.8 Pathophysiology

Burney et al. give a thorough and well written summary "Pathogenesis and pathophysiology of endometriosis" from *Fertility and Sterility Vol 98. No3. September 2012.* They define endometriosis as "an inflammatory, estrogen-dependent condition associated with pelvic pain and infertility" with multiple theories related to the "origin and molecular basis" of its disease process. Taken from their article, Fig. 4 demonstrates most of the current theories on the pathogenesis of endometriosis, the most well-known being Sampson's theory of retrograde menstruation. Support for this therapy lies not only in laparoscopic studies of healthy women with patent fallopian tubes identifying retrograde menstruation in 90% of these patients, but also from observed correlations between women with mullerian malformations and the increased prevalence of endometriosis among them. Obstructive outflow pathology of mullerian malformations leads to "back flow" of endometrial tissue through the fallopian tubes into the intraabdominal peritoneal cavity. The observed areas of implantation of likely retrograde endometriotic tissues presents commonly in the posterior cul-de-sac, ovaries, and tubes. Additionally, there are other factors include genetic susceptibilities, endocrine responses, immune system activation, epigenetic modifications, and a emybrologic origin of endometriosis (Signorile and Baldi 2010).

Proliferation of endometrial cells in the peritoneal environment causes not only an activation of inflammatory markers but also a change in both the nature of the endometrial cells and the surrounding peritoneal cells. Physical evidence of these changes correlates to various scar tissues on the peritoneum that are seen during surgical visualizations. These lesions are often described by their coloring – black, red, white or by the

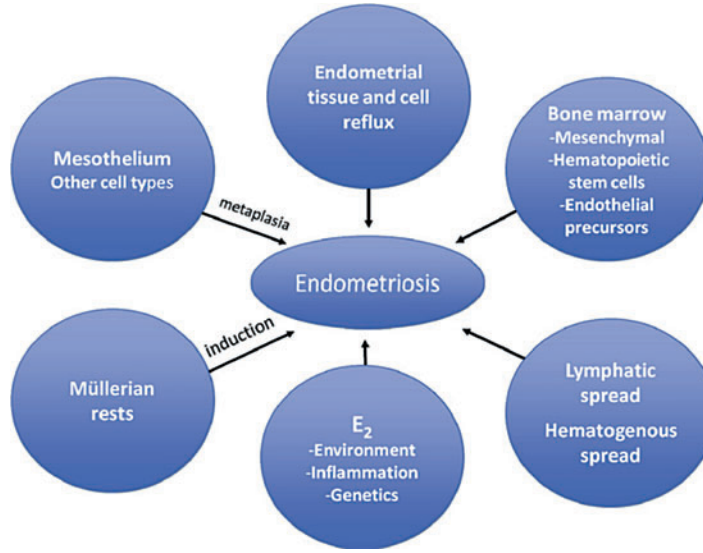

Fig. 4 Theories regarding endometriosis pathogenesis (Reprinted with permission Burney and Giudice 2012)

presence of adhesive tissue between pelvic organs.

Infertility in patients with endometriosis is thought to be due to several factors including tubal scarring and blockage leading to the interrupted passage of a mature ovum and unfavorable hormonal/inflammatory environment for either fertilization or implantation. De Ziegler et al. break up the pathophysiology of infertility secondary to endometriosis into three categories (Fig. 5): pelvic fluid within the pelvic cavity, ovarian function at the level of the ovary, and the endometrium (De Ziegler et al. 2010). Activation of inflammatory markers leads to a change in the peritoneal fluid which baths the reproductive organs. The most favorable location of fertilization is the ampullary region of the fallopian tube, an area that is open to the exposure of free peritoneal fluid. Altered ovarian function specific to endometriosis patients has yet to have an explanation or description of a specific pathologic process. Scientists have reported that endometriosis increased production of estradiol through prostaglandins as well as an abnormal response to progesterone.

Endometriosis often has a misalignment between disease severity and symptom complaint. A disease state found in an individual may be replicated in another individual but it may not confer the same or even similar symptoms. This divergence between pathophysiology and clinical presentation is reflected within the multiple efforts to create a staging system for endometriosis similar to a cancer staging system. Although the American Society of Reproductive Medicine (ASRM) has the longest standing staging system for endometriosis, it has been fraught with limitations because of the noncorrelation between disease stage and symptom presentation (Pearce et al. 2012). In addition, there is a lack of prognostic value. The primary benefit to the ASRM system has been within the realm of research and repeat surgical assessments.

In 2010 Adamson and Pasta introduced a validated revision of the ASRM endometriosis staging system that is designed to correlate with non-in-vitro fertility treatment outcomes and give clinicians an opportunity to counsel patients on possible anticipated outcomes (Adamson and Pasta 2010). They describe a scoring system where an endometriosis fertility index, using history, surgical findings and functional assessment of tubes and ovaries is calculated. This index is then used to correlate with non-in-vitro fertility treatment outcomes (Fig. 6).

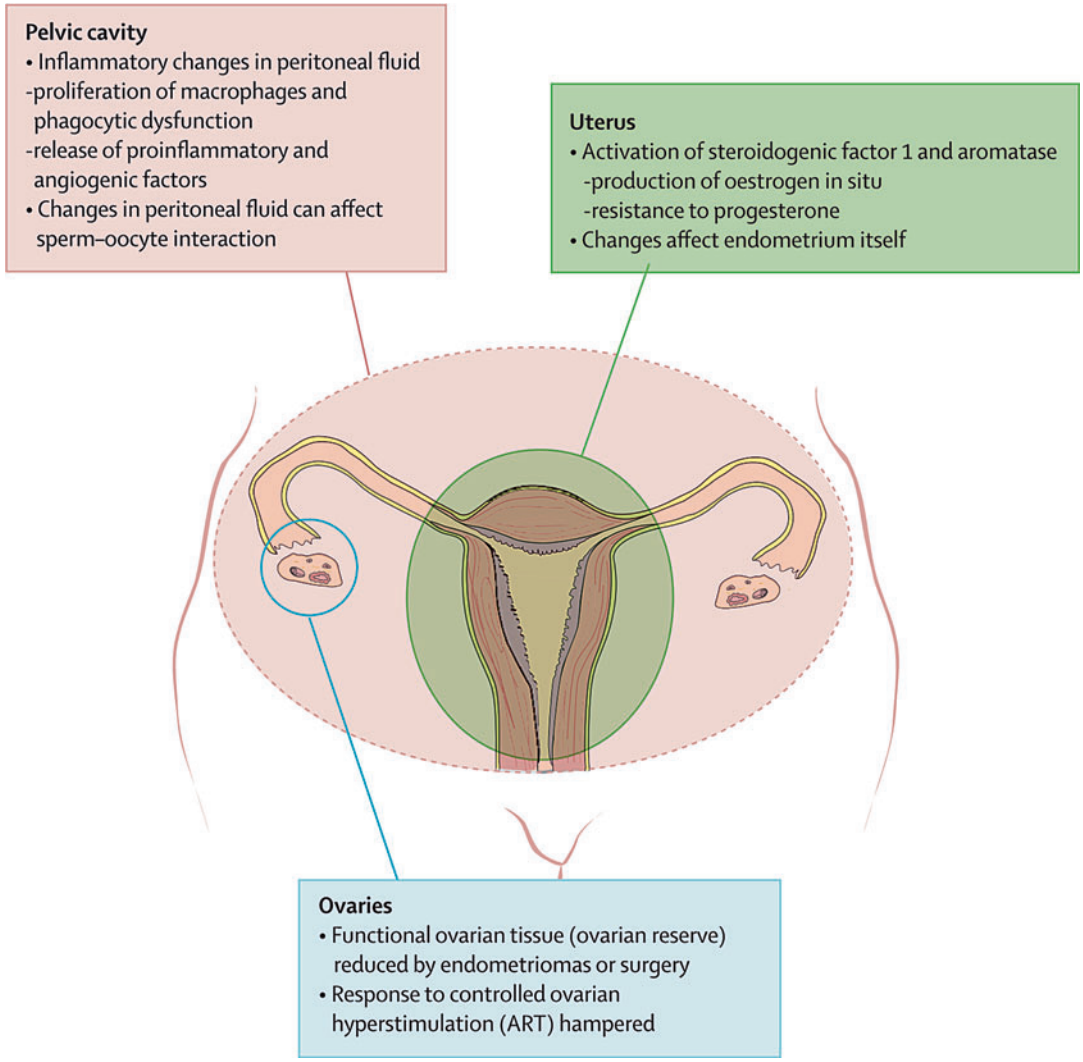

Fig. 5 Effects of endometriosis on human reproduction (Reprinted with permission De Ziegler et al. 2010). ART: assisted reproductive technologies

3.9 Management of Endometriosis: Pelvic Pain

The two complaints associated with endometriosis, pelvic pain and infertility, usually require a different approach during the initial patient interview and assessment. To begin, it may be more approachable to start with those patients who have complaints of pain and then move to those who present with infertility. While the emotional carriage which will accompany both complaints may be similar, the details of history and eventual investigations will vary based upon the patient's primary complaint and goals.

The defining pain description of endometriosis is cyclic pelvic pain, otherwise traditionally known as dysmenorrhea. Dysmenorrhea is pain associated with menses and can be separated into two categories: primary versus secondary. Primary dysmenorrhea occurs in about 40% of menstruating teenagers and is not consistently related to endometriosis. The pathophysiology linked to primary dysmenorrhea focuses on the prostaglandin pathway stimulated by the shedding of the

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description
4	= Normal
3	= Mild Dysfunction
2	= Moderate Dysfunction
1	= Severe Dysfunction
0	= Absent or Nonfunctional

	Left	Right
Fallopian Tube		
Fimbria		
Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Score	Left	+	Right	=	LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors	
Factor	**Description**	**Points**	**Factor**	**Description**	**Points**
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total Score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total Score is ≥ 71	0
Total Historical Factors			**Total Surgical Factors**		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:	Historical	+	Surgical	=	EFI Score

Fig. 6 Endometriosis fertility index surgery form (Reprinted with permission Adamson and Pasta 2010)

endometrial lining rather than the implantation of ectopic endometrial tissue.

The cyclic pelvic pain most consistently correlated with endometriosis falls into the category of secondary dysmenorrhea, implying that there was a period in which the patient had menses without pain. This detail becomes essential in differentiating between treatment options and diagnostic options from an empiric approach. Traditionally it is thought that pain associated with endometriosis occurs a day or two prior to the start of menstruation; however, it is not consistently demonstrative of endometriosis highlighting the variation between pathology and clinical manifestation. Other descriptions of pain associated with a disease process suggestive of endometriosis are pain with defecation particularly if it worsens during menses and dyspareunia. This pain may or may not be cyclic but usually worsen during menses, the most symptomatic time of the endometriotic implants. Some endometriosis presents with variable or constant, noncyclic, generalized or localized pelvic pain.

Since endometriotic tissue responds to hormonal changes, hormonal modulation is the primary medical therapy. The Mirena IUD or progestin dominant OCPs are the primary first line medical agents used to suppress pain symptoms. Gonadotropin agonists or antagonists, NSAIDs, progestin only pills, depo-provera, contraceptive implants, surgical resection are also options (Table 5).

Table 5 Review of standard medical therapeutic recommendations, their benefits, and common concerns (Vercellini et al. 2011)

Medical therapy options	Benefits	Limitations/concerns
Combined oral contraceptives	Ease of prescribing, prevalent, effective in both cyclic and continuous fashion, diversity of hormonal combination to assist with side effect control	Cannot be used when estrogen is contraindicated
Levonorgestrel-releasing intra-uterine devices	One time administration, long duration of effectiveness, may induce amenorrheic state	Requires trained personal to place, implant within body
Progesterone only oral therapy (i.e., norethindrone acetate)	Ease of prescribing, minimal interaction with other medications, minimal estrogenic side effects	Daily dosing required
Progesterone-based intramuscular injections	Three-month administration, very effective suppressor of endometrial gland proliferation	Office based administration required, bone density changes occur during therapy
GnRH analogues	Three-month administration, very effective suppressor of endometrial gland proliferation	Prominent hypoestrogenic side effects
Danazol	Very effective suppressor of endometrial gland proliferation	Prominent androgenic side-effects: acne, hirsutism, etc.

3.10 Management of Endometriosis: Infertility

When investigating complaints of infertility, a review of definitions is beneficial. Infertility in patients less than 35 years of age is a period of greater than 12 months of regular timed intercourse without contraception that is not marked by pregnancy (note that it is merely pregnancy and not delivery that drives this definition). While a patient who is 35 years of age or greater may be considered to have issues of infertility if that period is greater than 6 months. The urgency of investigation and exploration of patients presenting with infertility complaints increases as they age (refer to the chapter on infertility for details).

The physical examination in a patient with a suspicion for endometriosis does not vary greatly from the physical exam of a patient with general complaints of chronic pelvic pain. On the bimanual assessment, attention should be paid to the mobility of the uterus in comparison to the anterior abdominal well, adnexas, and rectum. Rectovaginal assessment may add information related to obliteration of the posterior cul-de-sac and/or dissection of the endopelvic fascia between the rectum and vagina.

- Thus far serum markers for endometriosis have been more experimental rather than practical (Burney and Giudice 2012). Clinically, the most common serum marker has been CA 125 in the setting of an endometrioma (endometriotic mass of the ovary). As often noted in the literature specific to CA 125, this is a serum marker which is nonspecific and thus frequently elevated in cases of endometriosis in general. Still there appears to be a role not only serially as with the cases of concurrent ovarian malignancies (Pearce et al. 2012) but also possibly for disease monitoring and therapy (Mol et al. 1998).
- Ultrasonography has had more clinical impact than the investigations into serum markers. General pelvic assessment with ultrasound for ovarian masses, endometriomas, has become undisputed in the initial investigation and assessment of patients for which suspicion for endometriosis is high.
  - Clinicians who specialize in endometriosis often recommend transvaginal ultrasonography to assess for invasive endometriotic lesions on the bladder and bowel allowing for a noninvasive manner of confirming a diagnosis of severe endometriotic disease as well as monitoring disease progression (Young 2014).

- CT or MRI may be useful to assess local tissue invasion but are not necessary for the initial assessment of endometriosis.

Medical therapy primarily utilizes the pathophysiologic understanding that endometriosis is a disease that responds to hormonal fluctuations. Thus if the cyclic nature of estrogen and progesterone can be controlled, it is assumed that the disease progression and impact of endometriosis can also be controlled. Standard medical therapeutic recommendations, their benefits, and common concerns are reviewed in Table 5 (Vercellini et al. 2011).

Other medical options have demonstrated potential in managing endometriosis through other molecular pathways: aromatase inhibitors (decreasing conversion of sex steroids to estrogen), immunomodulators and anti-inflammatory drugs (decreasing immune response and cytokine stimulation of pain pathways), anti-angiogenic therapies (blocking vascular endothelial growth factor in order to limit the invasive growth of ectopic endometrial tissue), and selective progesterone receptor modulators (blocking the effect of progesterone, primarily, and estrogen, secondarily, on reproductive tissue). All these options while available are generally considered after standard hormonal modulatory therapy has been exhausted.

Surgical intervention can be divided into two aspects: conservative, implying fertility preservation, versus radical with complete removal of all reproductive organs. With the advancement of minimally invasive techniques (laparoscopic and robotic) and instruments, the ability to offer fertility preserving surgery has increased and become more ubiquitous. Complete removal of uterus with ovaries and tubes is reserved for those not seeking fertility. While it has a high success rate in relieving pain complaints, surgically induced menopause is associated with adverse changes in the vagina, bladder, brain, joints, vascular system, and bone. Postoperative problems with menopausal symptoms, mood disorders, bladder problems, vaginal atrophy, and sexual problems, along with higher rates of cardiovascular disease, osteoporotic fractures, CNS diseases, and death rates in women with premenopausal removal of ovaries are reported. Some individuals who have undergone radical therapy may still have microscopic disease that is symptomatic requiring further therapy. Extensive counseling.

3.11 Reassessment

Chronic pelvic pain patients require close monitoring during early treatment and any period of uncertainty. While the frequency of close monitoring may differ depending upon overall assessment and treatment plan, a monthly follow-up for the first couple of months adds an early reassessment of treatment effectiveness and importantly adds to patient rapport and trust. At the point in the therapeutic process that the patient's pain symptoms have improved or are resolved, lengthening of the interval of follow-up is appropriate. However, if the patient's symptoms continue, worsen, or change in nature, a reassessment process mirroring the initial visit inquiry should be utilized and follow-up shortened and maintained appropriately.

4 Conclusion

The changing course of terminology and understanding of pain physiology cannot be stressed sufficiently. As terminology becomes more precise, the need increases to accurately specify a more specific etiology of pelvic pain based on this terminology. Matching clinical findings with a detailed history, directed physical and pelvic exam, appropriate laboratory, or radiologic assessment facilitates this process. Such a transition in describing and diagnosing pelvic pain will allow for more systematic and algorithmic approaches to treatment.

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Management of Benign Breast Disease

Heather R. Macdonald

Contents

Abstract

The purpose of identifying and treating benign breast disease is twofold: to identify underlying breast cancer or exclude its presence and treat symptoms. The most common breast complaints are breast masses, breast pain, nipple discharge, and breast infections. A palpable breast mass should be evaluated by the triad of clinical breast exam (CBE), imaging (ultrasound in all patients with the addition of mammogram in patients over 30), and biopsy. Mastalgia is the most common breast complaint. A thorough evaluation should be performed to exclude malignancy. Nipple discharge may be physiologic, especially if bilateral, multiple ducts, seen only with expression and clear, green, or black. Medications, especially centrally acting or psychotropic drugs, and nipple stimulation are potential causes of non-pathologic discharge. Nipple discharge that is spontaneous, unilateral, single duct, clear or bloody, or associated with a palpable mass is especially concerning for underlying malignancy. Mastitis is a common occurrence even in non-lactating women. Inflammatory cancer must be ruled out, especially in an inflammation not responding to antibiotics and supportive measures. Lactating women with a breast infection must drain the breast regularly to prevent milk stasis that encourages bacterial growth. Antibiotic therapy should be guided by what is safe for the nursing infant. Skin flora is the most common pathogen.

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Referral for specialty services should be provided to patients with atypical biopsies, discordant biopsies, breast cancer, biopsy findings that require excision, nonhealing abscesses, and hereditary breast and ovarian cancer syndromes.

Keywords
Clinical breast exam • Breast mass • Fibroadenoma • Mastalgia • Nipple discharge • Mastitis • Galactorrhea

1 Introduction

The purpose of identifying and treating benign breast disease is twofold: to identify underlying breast cancer or exclude its presence and treat symptoms. Breast complaints are common in gynecologic practice, and benign breast conditions are within the scope of practice of a general ob-gyn. Referral for specialty services should be provided to patients with atypical biopsies, discordant biopsies, breast cancer, biopsy findings that require excision, nonhealing abscesses, and hereditary breast and ovarian cancer syndromes. Elsewhere in this book, breast cancer screening in the asymptomatic woman is described. This chapter will focus on the evaluation and treatment of the symptomatic patient. Focus will be on the most common breast complaints: breast masses, breast pain, nipple discharge, and breast infections. Table 1 lists conditions for which specialty care is required, and the patient should be referred.

Table 1 Indications for referral to a breast specialist

Indications for referral to a breast specialist
Atypical breast biopsy
Malignancy
Histologic findings on biopsy that require excision
Nonhealing breast abscess or inflammation
Familial breast cancer syndromes
Discordant breast biopsy results

1.1 Clinical Breast Exam

Clinical breast exam (CBE) should be part of a well woman health evaluation. The American College of Obstetricians and Gynecologists recommends women undergo CBE every 1–3 years between ages 20 and 39 and every year after age 40. If the patient is still menstrual, the ideal time to perform the exam is immediately after menses when breast tissue is most quiescent.

The clinical breast exam should encompass all breast tissue from the clavicles to the inframammary folds and from the midaxillary lines to the sternal borders. Axillary and supraclavicular lymph nodes should be included in the field of examination. On clinical breast exam, dominant masses should be described by size, position on the clockface (with the nipple at the center, 12 o'clock superior, 6 o'clock inferior, etc.), and distance from the nipple (e.g., 2 cm mass at 4:00 3 cm from the nipple). The mobility of the lesion or lack thereof should be described as well as any overlying skin changes. The presence or absence of lymphadenopathy in the axillary or supraclavicular beds should be noted. Findings on clinical breast exam concerning for malignancy include tethering to the skin or underlying muscle, relative immobility of the mass, irregular or indistinct borders of a dominant mass, the presence of a mass with single duct bloody nipple discharge, overlying skin changes including erythema or induration, and the presence of axillary or supraclavicular adenopathy.

1.2 Palpable Mass

A palpable mass is a three-dimensional finding distinct from the surrounding breast tissue and is a common breast complaint. When a patient presents with suspicions of a palpable mass, she should be asked to describe when and how it was first discovered, how long it has been present, and if it is still palpable, does it change with her menstrual cycle, has she appreciated it before (i.e., does it come and go), is it painful, are there skin changes or nipple discharge, and has she had a breast mass previously in either breast. Masses

Table 2 Pertinent findings when documenting a breast mass

Pertinent findings when documenting a breast mass
Laterality
Location expressed as clockface position and distance from the nipple
Size
Associated skin changes (edema, erythema, retraction)
Fixation
Texture (smooth, lobulated)
Tenderness
Presence or absence of axillary or supraclavicular lymphadenopathy

that wax and wane with menstrual cycles are consistent with fibrocystic changes and are rarely pathologic. History of a previous breast cyst or fibroadenoma may be informative as patients are at risk for additional lesions. Alternatively a palpable mass in conjunction with bloody nipple discharge is highly concerning for carcinoma. Overlying skin changes indicate an inflammatory process but can also be concerning for inflammatory carcinoma.

Table 2 describes what should be documented when examination reveals a mass distinct from the surrounding breast tissue. A palpable breast mass should be evaluated by the triad of clinical breast exam (CBE), imaging (ultrasound in all patients with the addition of mammogram in patients over 30), and biopsy. Even in recent series, between 9% and 22% of palpable breast cancers were not apparent on breast imaging (Morrow 2000). In young patients with a benign clinical breast exam and benign appearing imaging (BIRADS 2), tissue sampling may be omitted, but as breast carcinoma or cancerous lesions metastasizing to the breast (lymphoma, sarcoma) can present in teenaged patients, careful consideration should be given to securing a definitive diagnosis of any dominant mass with tissue sampling. Tissue sampling should be accomplished with a needle wherever possible (Silverstein et al. 2009). Surgical excision of a previously unsampled breast mass should be rare. The majority of lesions will be benign and unlikely to need excision. The uncommon malignant lesion will not be completely treated by simple excision (if breast cancer) or may not be treated surgically at all (if lymphoma or metastatic sarcoma). A concordant diagnostic triad of benign CBE, benign imaging, and benign biopsy carries a false-negative rate (or the chance that an underlying cancer may be missed) of less than 1% (Ariqa et al. 2002). Concordance of all three elements of the diagnostic triad is key. Any discordance between the clinical exam, imaging impression, and biopsy results should trigger a second biopsy or surgical excision.

Management of the lesion is guided by the biopsy results. Asymptomatic benign masses less than 3 cm in size can be followed with ultrasounds to demonstrate stability every 6 months for 2 years. Any patient who is bothered by the sensation or presence of a mass should be offered excision. Surgical excision should be considered for lesions larger than 5 cm due to sampling concerns as breast lesions can be heterogeneous. Additionally, larger lesions can be cosmetically destructive even if benign and are better excised before they require more extensive if not reconstructive surgery. If atypia is identified within any lesion, surgical excision is warranted for definitive diagnosis and cancer risk reduction. Table 3 summarizes benign breast histology by risk of breast cancer as well as treatment considerations. Not all lesions listed will present as a palpable mass. For example, radial scar is most often identified by stereotactic core biopsy after a mammographic finding. However they are including Table 3 as a reference for interpreting breast biopsy results.

Table 4 includes benign causes of palpable breast abnormalities and recommendations for management. Common benign causes of palpable breast masses include simple cysts and fibroadenomas. Cysts appear as empty black circles on ultrasound as cyst fluid allows free passage of ultrasound waves without reverberating back to the transducer. They often grow suddenly and are painful at first detection. They may be symptomatic with menses. They may be aspirated to alleviate tenderness. Cyst fluid should only be sent for cytology only if it is frankly bloody, as analysis of cyst aspirate has not been shown to be sensitive or specific for malignancy (Ciatto et al. 1987). Green, black, dark brown, yellow, and clear fluid

Table 3 Breast histology stratified by risk of breast cancer

Breast histology	Lifetime risk of breast cancer	Therapeutic considerations
Carcinoma in situ	High risk	Breast oncologic care
(DCIS, LCIS)	30–50%	
Proliferative lesions with atypia	Intermediate risk	Surgical excision
Atypical ductal hyperplasia	15–30%	Consider chemoprevention
Atypical lobular		
Proliferative lesions without atypia	Low risk	Annual mammography may consider surgical excision; excise if symptomatic, biopsy discordant, or diagnosis in doubt
Fibroadenoma	<15%	
Moderate/florid ductal hyperplasia of the usual type		
Radial scar/complex sclerosing lesion		
Papilloma		
Papillomatosis		
Sclerosing adenosis		
Flat epithelial atypia		
Nonproliferative lesions (cysts)	Minimal to no increase risk	No intervention indicated
Duct ectasia		May aspirate or excise if symptomatic
Papillary apocrine changes		Note: excise lipoma if >5 cm
Non-sclerosing adenosis		
Periductal fibrosis		
Mild epithelial hyperplasia of the usual type		
Lipoma		

may be discarded. After cyst aspiration if any mass remains, it should be biopsied to avoid missing the solid component of a complex cyst. Cysts should only be surgically excised if they recur after multiple aspirations.

Table 4 Common causes of palpable breast masses and management

Histology	Management
Breast cyst	Observation; aspiration if painful
Fibroadenoma	Observation if asymptomatic <3 cm
	Excision if atypical, symptomatic or >3 cm
Fibrocystic change	Observation
Proliferative fibroepithelial lesion	Repeat sampling with needle biopsy or excision to rule out phyllodes tumor

Fibroadenomas are the most common solid benign mass, occurring in up to 25% of asymptomatic patients (El-Wakeel and Umpleby 2003). Fibroadenomas are biphasic lesions with both epithelial and stromal components. They belong to a family of lesions that include benign phyllodes tumors and cystosarcoma phyllodes. They frequently are nontender, firm, and very mobile and do not change with menses. Lesions less than 3 cm may be followed expectantly or excised based on patient preference. Many patients with fibroadenoma will form more than one lesion and may not desire multiple excisions. Fibroadenomas larger than 5 cm raise the suspicion of a phyllodes tumor. Larger lesions may be undersampled by needle biopsy and should be excised. Preoperative needle biopsy remains important however because a known phyllodes tumor is excised with a 1 cm margin to minimize recurrence, whereas a known fibroadenoma is not. In fact the compressed pseudocapsule of breast tissue that surrounds a fibroadenoma is carefully preserved at excision as it will decompress, often by the time the skin is closed, to fill in the defect left by the excised lesion. Phyllodes tumors even if benign are always excised as they are locally aggressive and cosmetically destructive.

The management of breast cancers, carcinomas or sarcomas, is beyond this chapter.

1.2.1 Breast Pain

Mastalgia is the most common breast complaint (Morrow 2000). It is more common among premenopausal patients than postmenopausal. Association with an underlying cancer is unusual but

not impossible: in one series 16% of 240 patients with breast cancer presented with pain alone as an initial symptom (Preece et al. 1982). Concern for an underlying cancer may be what prompts the patient to seek medical attention, and a thorough evaluation should be performed to exclude malignancy.

Cyclic mastalgia is generally described as a dull heaviness, worsened with pressure and movement and poorly localized. It may radiate to the axilla or shoulder. It may be alleviated with anti-inflammatory medications. Noncyclic mastalgia is unrelated to timing of the menstrual cycle and is more common in the 40s and 50s. It may also be poorly localized and may not respond to over-the-counter medications. The underlying cause of breast pain is unknown. Premenstrual mastalgia suggests a hormonal cause, but no fluctuations or abnormalities of serum estrogen or progesterone levels have been shown to be associated with breast pain. Overuse of caffeine has also been postulated, but three studies looking at caffeine exposure and restriction in response to breast pain, including randomized control trials, have not demonstrated an association (Allen and Froberg 1987).

In eliciting a history from a patient with breast pain, the duration and character of the pain should be characterized, as well as its location and relationship to the menstrual cycle. Any patient with recently missed menses should be evaluated for pregnancy as breast pain can be an initial symptom of a recently pregnant patient. The evaluation of mastalgia includes a clinical breast exam and a screening mammogram if the patient is over 35. Younger women may be appropriately evaluated with clinical breast exam alone without imaging if the exam is normal. Any palpable abnormality should be evaluated with ultrasound and possibly biopsy. Focal areas of tenderness may be ultrasounded to detect an underlying cyst too deep to appreciate on exam. Mastalgia is often self-limiting, resolving spontaneously in 3–6 months up to 80% of cases (Orr and Kelley 2016). Patients for whom the pain is severe enough to interfere with daily life and for whom it has persisted beyond the 3–6-month window expected for spontaneous resolution are candidates for intervention. Table 5 outlines treatment options for mastalgia. The only FDA-approved medication for breast pain is danazol, an anti-gonadotropin. Response rates in clinical trials approached 75% for both cyclic and noncyclic breast pain at doses of 100–400 mg/day, with a slightly better rate seen in noncyclic pain patients (Mansel et al. 1982). Side effects include virilizing symptoms including deepening voice, weight gain, acne, and male-pattern hair loss and hair growth and limit its acceptability to patients. Tamoxifen a mixed estrogen receptor agonist/antagonist can be tried in an off-label manner for 3–6 months. It blocks estrogen stimulation of the breast. Small studies of 10–20 mg daily have demonstrated pain relief (Fentiman et al. 1986; Messinis and Lolis 1988). Side effects include vaginal discharge, irregular uterine bleeding, and hot flushes. Long-term use has been associated with increased thromboembolic events, endometrial stimulation including hyperplasia and cancer, and cataracts.

Table 5 Treatments for breast pain

Agent	Comments and side effects
NSAIDs	Short-term efficacy
Evening primrose oil	Equivalent to placebo in randomized control trials
Danazol	Only FDA-approved medication for mastalgia
	Side effects: acne, androgenic (male-pattern weight gain and hair growth and loss, deepening voice)
Bromocriptine	Off-label use
	Decrease prolactin and stimulation of the breast
	Side effects: dizziness, potential for seizure if stopped suddenly
Tamoxifen	Off-label use
	Estrogen antagonist at the breast
	Off-label use
	Side effects: menopausal symptoms, irregular vaginal bleeding due to endometrial stimulation; rare (VTE, cataracts, uterine cancers)

For patients wanting to try a herbal approach, evening primrose oil has been studied to treat breast pain with mixed results that mimic placebo effect; however, side effects were rare (Morrow

2000). Studies investigating caffeine restriction and vitamin E supplementation showed no benefit. Surgery has no role in the treatment of breast pain outside the excision of a tender mass.

1.2.2 Nipple Discharge

Nipple discharge can be divided into physiologic discharge, potentially pathologic discharge, and discharge due to an underlying endocrine disorder or medication use. Single duct spontaneous clear or bloody nipple discharge is concerning for underlying breast pathology and should be worked up rigorously. The most common cause of spontaneous bloody nipple discharge is a benign intraductal papilloma, but an underlying ductal carcinoma must be ruled out.

Key questions to ask when taking the history of a patient complaining of nipple discharge include the color of the discharge, with bloody or clear being most concerning and black or green being most likely physiologic. The patient should be asked to describe whether it is spontaneous or seen only with expression or manipulation of the nipple. If the patient has seen the discharge as it exists the nipple, she should be asked if it extrudes from one duct or several, with physiologic discharge seen at multiple points on the nipple. Single duct spontaneous discharge is most concerning. Table 6 describes pertinent characteristics that discern physiologic discharge from pathologic.

Table 6 Characteristics of nipple discharge

Likely physiologic discharge	Likely breast pathology	Consider endocrinopathy or medication cause
Bilateral	Unilateral	Unilateral or bilateral
Multi-duct	Single duct	Multi-duct
Seen with expression only	Spontaneous	Spontaneous
Clear, green, brown, black	Clear or bloody	Milky
History of nipple stimulation	No history of nipple stimulation	No history of nipple stimulation
	Presence of a palpable mass	Menstrual irregularities

On clinical breast exam, the examiner should perform the exam as usual but then sweep all four breast quadrants with an eye on the nipple to note where pressure on the breast elicits the discharge. If discharge is expressed, the area of the breast being examined when the discharge was seen should be noted, as well as the color and how many ducts it involves. In the past, discharge has been sent for cytology. Studies have shown low sensitivity and specificity of cytologic studies of nipple discharge, so the test should no longer be ordered. Nipple discharge most concerning for underlying malignancy is single duct spontaneous clear or sanguineous discharge associated with a palpable mass. Workup includes diagnostic mammography, retroareolar ultrasound on the affected side, and biopsy of any identified lesions. If exam, mammogram, and ultrasound fail to identify a source, a ductogram may be considered. By injecting a radiopaque dye into the affected ductal system, a filling defect on subsequent mammogram may identify an intraductal mass. The ductogram is limited in its ability to localize and biopsy a lesion however. In the past decade, ductogram has largely been replaced by breast MRI with and without contrast, as lesions can be localized and biopsied with MRI guidance.

Physiologic nipple discharge is common with repeated nipple stimulation, for example, with rigorous routine self breast exam, sexual activity, or nipple piercing or accessories. Once discharge is seen, some patients may feel a sensation of fullness behind the nipple that is alleviated by expressing the discharge, and others may feel compelled to express discharge in an effort to keep the area clean. By repeatedly expressing or checking for discharge, they are reinforcing its production and increasing its occurrence. The color is often black, brown, green, creamy, or clear and usually is elicited from more than one duct in the nipple. Retroareolar ultrasound may identify dilated ducts or duct ectasia. Green or black multi-duct nipple discharge that is seen only with expression from the nipple is not pathogenic but may be unnerving for the patient. Careful explanation of the mechanism of nipple stimulation to increase fluid production from the

nipple and breast is important for patient reassurance, and treatment is cessation of nipple stimulation to diminish fluid production.

Galactorrhea, or bilateral milky or creamy nipple discharge, usually identified in the absence of breast stimulation and coming from multiple ducts in both breasts is suggestive of an underlying endocrine disorder. Both prolactin-secreting tumors and hypothyroid disorders can present with galactorrhea. Please see the chapter entitled "► Hyperprolactinemia, Galactorrhea, and Pituitary Adenomas" for a more detailed discussion of galactorrhea. History and physical should focus on symptoms and signs of endocrinopathy including infrequent or absent menses, headaches, bitemporal vision loss, changes in appetite and weight, dryness of the hair and skin, and depressed energy and mood. Lab studies should include TSH and prolactin. If prolactin is elevated, a brain MRI focused on the sella turcica for pituitary lesions should be obtained and the patient referred for specialty care. Treatment may involve resection or medical therapy with antiprolactin medication like bromocriptine.

Nipple discharge may also be related to medication use, particularly psychotropic medications. A careful medication history should be taken with attention paid to medications started or stopped in coincidence with onset of discharge.

1.3 Mastitis

Mastitis or inflammation of the breast can be due to several underlying causes: an acute peripheral abscess, a subareolar or periareolar abscess or fistula, granulomatous mastitis most commonly idiopathic in this country, or inflammatory breast cancer. Each has distinct presentation, treatment, recurrence risks, and workup.

Mastitis is most commonly due to a bacterial infection. The most common pathogen is *Staphylococcus aureus* or skin flora. Antibiotic treatment is often initiated after a presumptive diagnosis of bacterial infection is made, but careful follow-up within 1 week is warranted to exclude a missed diagnosis of breast cancer. Risk factors for breast infections and abscesses in non-lactating women include diabetes, smoking, and obesity. Common presenting symptoms are pain, redness, warmth, and fever. On physical exam, the affected breast is warm to touch, erythematous, and tender. An associated mass suggests an underlying abscess, and a breast ultrasound should be ordered for further evaluation. Abscesses smaller than 5 cm are often amenable to needle drainage; larger abscesses may require surgical incision and drainage. Antibiotic coverage should vary by local sensitivities, but Table 7 lists suggested targeted therapies to common pathogens. Patients should be followed closely for several weeks to ensure response to treatment. A clinical diagnosis of mastitis that does not respond to appropriate antibiotic treatment should be reevaluated for underlying malignancy. Ultrasound may be used to identify an underlying mass or lymph node for needle biopsy. If pus is encountered, it should be cultured for pathogen and sensitivities as antibiotic resistance is a growing problem.

Table 7 First-line antibiotic therapy for mastitis

Condition	Therapy
Mastitis	Dicloxacillin, cephalexin
If penicillin allergic	Clindamycin, erythromycin
If MRSA is suspected or confirmed	Trimethoprim-sulfamethoxazole double strength, clindamycin

Bacterial infections of the breast are common in 10–20% of patients who are postpartum or nursing but may occur in otherwise healthy non-lactating women. Risk factors include milk stasis, blocked ducts, ineffectual infant feeding due to latch issues or poor suck, stress, tight-fitting clothes or bras, or skin irritation and breakdown. Clinical presentation is similar to breast infections in non-lactating women. Treatment includes antibiotics, warm compresses to encourage milk expression, and aggressive massage and nursing (or pumping) to alleviate milk stasis. Antibiotic therapy should include aerobic and anaerobic coverage and should be with an agent safe for breastfeeding (see Table 7). Continuation of breastfeeding should be encouraged as prevention of milk stasis is of paramount importance to clear the infection. Infants are

more effective at draining the breast than pumps. Mothers can be reassured the breast infection does not pose a risk to her infant due to mother's immunity present in the milk, antibiotic present in the milk, and an infant's gastrointestinal immune defenses. If the mother chooses to stop breastfeeding, often due to discomfort, she should be educated she needs to continue to drain the breast with hand expression or a pump until the infection resolves. If an abscess is present, it should be treated similarly to that in a non-lactating patient. She should be counseled regarding the rare risk of milk fistula formation but be reassured most spontaneously resolve with cessation of breastfeeding.

Peri- or subareolar abscesses are a distinct entity from peripheral breast abscesses. Patients will present with a painful subareolar infection that commonly fistulizes with drainage of pus from a defect at the periareolar border. They are frequently recurrent. Smoking is an important risk factor (Orr and Kelley 2016). The pathogenesis is thought to be squamous metaplasia of the terminal ductal epithelium with intussusception of secretions leading to infection and abscess formation. Acute abscesses should be treated with drainage if not draining already and antibiotics. When the inflammation has subsided, a duct excision via a radial incision is indicated to remove the occluded duct and excise the fistulous tract to prevent or treat a chronic fistula.

Every nonhealing abscess should be evaluated with biopsy of the abscess wall to rule out inflammatory breast cancer. If no breast mass is identifiable by exam or imaging, the leading edge of skin erythema should be sampled with a punch biopsy. Inflammatory breast cancer can be readily identified by tumor cells in the dermal lymphatic system, creating the classic peau d'orange skin appearance of thickened erythematous skin with dimpled appearance. Inflammatory breast cancer is a poorly differentiated aggressive breast cancer that is systemic at its inception and carries a poor prognosis. The patient should be referred immediately to oncology for chemotherapy.

Rarely biopsy may reveal granulomatous mastitis, caused by either fungal or tuberculosis infections in the developing world but more commonly idiopathic granulomatous mastitis (IGM) in the USA. IGM describes an even more rare condition that presents with acute inflammatory changes and abscesses in the absence of infection or malignancy. It is a diagnosis of exclusion with granulomas seen on biopsy but no TB or fungal infections identified on special staining. The natural history is that of spontaneously occurring and resolving breast abscesses. Effective treatment is unknown although short courses of steroids are often used to diminish inflammation.

2 Conclusion

Breast complaints are common and distressing to patients, both due to their symptomatology and an underlying cancer-related anxiety. The evaluation of a breast complaint should be thorough to detect or rule out breast cancer and if appropriate reassuring to the patient. We have discussed the most common causes of benign breast disease. Patient education regarding normal breast health and abnormal breast findings is important.

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Management of Uterine Fibroids

Valentina M. Rodriguez-Triana and William H. Parker

Contents

Abstract

Uterine fibroids are the most common tumors of the female reproductive tract. It is estimated that the incidence of fibroids by age 35 reaches 40 % for Caucasian women and 60 % for African American women (Baird and Dunson 2003). Most women with fibroids are asymptomatic; however, symptomatic fibroids remain the most common indication for hysterectomy. In 2010, approximately 196,735 hysterectomies were performed for fibroids in the United States (Wright et al., Obstet Gynecol 122 (2 Pt 1):233–241, 2013).

The location of fibroids in the uterus will often determine the type and severity of symptoms a woman will experience. The most common presenting symptoms include infertility, heavy menstrual bleeding, bladder pressure, and pelvic pressure. A thorough history and physical examination along with appropriate imaging can help the clinician tailor the treatment options to improve a patient's symptoms. As such, the management of fibroids is highly variable.

Expectant management of fibroids is a reasonable option for women who are asymptomatic or not bothered by their symptoms. Medical management can be used for patients desiring to avoid surgery or in preparation for surgery. The surgical management of symptomatic fibroids is broad and includes endometrial ablation, laparoscopic cryomyolysis, laparoscopic uterine artery occlusion,

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laparoscopic radiofrequency volumetric thermal ablation (LRVTA), myomectomy (abdominal, laparoscopic, or hysteroscopic), and hysterectomy. Radiology-based management options include uterine artery embolization (UAE) and MRI-guided focused ultrasound. Both the UAE and the MRI-guided focused ultrasound require consultation with radiologists.

Despite treatment options available, it is important for the clinician to recognize that not all fibroids require intervention. Counseling patients that fibroids do not have oncogenic potential may also help reassure them and guide their decision-making. Expectant management of fibroids in a stable woman is often an acceptable choice.

Keywords

Fibroids • GnRH agonist • Levonorgestrel intrauterine device • Mifepristone • Myomectomy • Morcellation • Hysterectomy • Endometrial ablation • Hysteroscopy • Uterine artery occlusion • Laparoscopic radiofrequency volumetric thermal ablation • Uterine artery embolization • MRI-guided focused ultrasound

1 Introduction

1.1 Pathology and Epidemiology

Fibroids are benign tumors of the myometrium. They are comprised of smooth muscle and contain large amounts of collagen, fibronectin, elastin, and proteoglycan (Leppert et al. 2006). They are surrounded by a pseudocapsule made of compressed smooth muscle and areolar connective tissue. In certain studies, fibroids have been detected in up to 77 % of all uteri removed during hysterectomy (Cramer and Patel 1990).

1.2 Risk Factors

Epidemiological studies have demonstrated certain risk factors for fibroid development. Increasing age is associated with increased probability of developing fibroids. It is estimated that the incidence of fibroids by age 35 reaches 40 % for Caucasian women and 60 % for African American women. By age 50, the incidence reaches 70 % for Caucasian women and 80 % for African American women (Baird and Dunson 2003). Race also plays a role in the development of fibroids, as African American women are more likely to be diagnosed with fibroids approximately 5 years earlier than white women (Huyck et al. 2008). The exact mechanism is still unknown, although it could be related to differences in estrogen levels, diet, and environmental exposures (Marshall et al. 1997).

Family history also plays a role in the development of fibroids, as women with a first degree relative with fibroids have a 2.5 times increased risk of developing fibroids themselves (Vikhlyaeva et al. 1995). Overweight women have a 21 % increased risk of having fibroids for every 10 kg increase in body weight (Ross et al. 1986).

Certain factors are thought to be protective from the development of fibroids and include late menarche, exercise of 7 h per week, increasing parity, and tobacco use (Baird et al. 2003, 2007; Lumbiganon et al. 1996; Marshall et al. 1998; Michnovicz et al. 1986; Parazzini et al. 1996).

1.3 Oncogenic Potential

Fibroids do not have oncogenic potential. They are monoclonal tumors that arise from myometrial smooth muscle and are genetically different from sarcomas. Genomic hybridization studies comparing sarcomas and fibroids have not found any shared anomalies between the two (Quade et al. 2004). There are certain leiomyoma variants that can demonstrate atypical behavior, but these tumors have a distinct histology and are not thought to originate from benign, typical fibroids. This becomes particularly relevant for women who opt for expectant management of their fibroids, as they should be counseled that their fibroids would not become cancerous if left untreated.

1.4 Effects on Fertility and Pregnancy

Intramural and subserosal fibroids have not been shown to adversely affect fertility. In a study examining the use of hysteroscopy to assess cavity distortion from intramural and subserosal fibroids, there was no improvement in ongoing pregnancy rates or live birth rates after removal of intramural and subserosal fibroids (Pritts et al. 2009). In this same study, however, women with submucous fibroids had a 70 % decrease in pregnancy and live birth rates, which slightly improved after resection. This data is important to consider when counseling patients who desire fertility and have a fibroid uterus, as improvement in fertility rates remains contingent upon the location of the fibroids.

Currently, there is no high-quality data to confirm the effects of fibroids on pregnancy; however, available data suggests that most women with fibroids will have normal pregnancy outcomes (Segars et al. 2014). Because of the relative paucity of data, it is not recommended that women with incidentally discovered fibroids undergo a myomectomy as part of preconception preparation.

2 Management of Uterine Fibroids

2.1 Clinical Evaluation

The goal of fibroid management and treatment is to improve overall quality of life, as their presence is rarely associated with any life-threatening emergencies. As such, a thorough evaluation of each patient will allow the clinician to provide treatment specific to a woman's symptoms and goals.

2.1.1 Patient History

Evaluation of fibroids begins with evaluation of symptoms, which can often give clues as to the location of the fibroids. The most common presenting symptom for women with fibroids is heavy menstrual bleeding. The degree to which the patient has heavy bleeding is typically related to the location of the fibroids. Submucosal fibroids are the most highly associated with heavy bleeding and are also more likely to cause symptomatic anemia (Puri et al. 2014). The mechanism for this is likely due to fibroid deregulation of certain factors that affect angiogenesis, which in turn leads to the formation of abnormal vasculature that is more likely to cause bleeding (-Stewart and Nowak 1996). Fibroids may also cause disrupted uterine contractions and impaired clotting mechanisms. Because the relationship between fibroids and heavy bleeding is variable, however, it is recommended that all women who present with abnormal uterine bleeding receive a full work-up, including screening for coagulopathies and other endocrinopathies. Because fibroids are not often associated with inter- menstrual and postmenopausal bleeding, women with these symptoms should undergo evaluation for underlying malignancies.

The relationship of fibroids to pain has not been clearly established in the literature. In a study evaluating 635 asymptomatic women to determine the presence of fibroids via transvaginal ultrasound, the 96 women who had fibroids were only slightly more likely to complain of cyclic pelvic pain and dyspareunia compared to those without fibroids (Lippman et al. 2003). The women with fibroids were also no more likely to have dysmenorrhea than women without fibroids. Pedunculated fibroids that have torsed on their stalk can cause acute pain, which often requires surgical intervention. Fibroid degeneration is also associated with pelvic pain. Enlarging fibroids may outgrow their blood supply, which leads to cell necrosis and death. This process can often be successfully managed with NSAIDS and expectant management.

Fibroids can be associated with pelvic pressure, bladder symptoms, and bowel complaints. Data looking at the effects of uterine artery embolization (UAE) on bladder symptoms demonstrated a 35 % reduction in mean uterine volume with a 86 % improvement in urinary frequency and urgency (Pron 2003). A separate study looking at women treated with GnRH agonist for 6 months demonstrated a 55 % decrease in uterine

volume with an additional decrease in urinary frequency, urgency, and nocturia (Langer et al. 1990). It is unclear from this data, if the symptom improvements were related to the medication or reduction in fibroid size.

As mentioned earlier, patients with submucous fibroids can present with infertility. Thus, women presenting with infertility as a complaint should be evaluated for intracavitary pathology with saline sonohysterogram, MRI, or hysteroscopy as part of their work-up.

There is no evidence to show that "rapid uterine growth," defined by uterine growth of 6-week size in 1 year, correlates with the presence of sarcoma. In one study evaluating the incidence of sarcoma in patients presenting with rapid growth, one of 371 patients were found to have sarcoma (Parker et al. 1994). A reanalysis of the pathologic criteria used for this study found that this one patient had, in fact, an atypical leiomyoma rather than a leiomyosarcoma. Patients presenting with "rapid uterine growth" merit thorough evaluation, but this finding does not imply cancer.

2.1.2 Physical Examination

Physical examination of patients with fibroids can often reveal size and location of fibroids and is essential when considering treatment options and planning a surgical approach.

Even for women with a BMI >30 cm/kg, a bimanual exam to assess uterine size has been shown to correlate well with the actual pathologic size and weight of the uterus (Cantuaria et al. 1998). Most clinically significant subserosal and intramural fibroids will be detected as bulky and irregularly shaped on physical examination (ACOG 2000).

As part of the evaluation, the clinician should assess the location of the top of the fundus. This will help determine the type of skin incision that is used for laparotomy or whether placement of an umbilical port would be feasible during laparoscopy. It is also important to determine how broad the uterus palpates in relationship to the pelvic sidewall. If the fibroid uterus feels very broad and difficult to be elevated off the sidewall, laparoscopic surgery may be more technically difficult.

2.1.3 Imaging

Imaging should be included as part of the evaluation of uterine fibroids. The most commonly used imaging modalities for fibroids are transvaginal ultrasound, saline-sonohysterography (SSH), and magnetic resonance imaging (MRI). In one study evaluating the preoperative use of transvaginal ultrasound, SSH, hysteroscopy, and MRI in patients who were scheduled to undergo hysterectomy for symptomatic fibroids, MRI was 100 % sensitive and 91 % specific at detecting submucosal fibroids (Dueholm et al. 2001). Transvaginal ultrasound had 83 % sensitivity and 90 % specificity, SSH had 90 % sensitivity and 89 % specificity, and hysteroscopy had 82 % sensitivity and 87 % specificity. MRI provides the additional benefit of identifying adenomyosis and adenomyomas (Dueholm et al. 2002a, b). Focal areas that appear not well delineated and that have high or low intensity signals within the myometrium are very characteristic of adenomyosis.

Of the above imaging modalities available for evaluation of fibroids, ultrasound continues to be the least expensive and most accessible. Fibroids on ultrasound appear as regularly shaped, hypoechoic masses. For uteri <375 cc with 4 or less fibroids, it is considered a very accurate imaging modality (Dueholm et al. 2002a).

When available, MRI provides greater accuracy for characterization of fibroids and is an essential tool for preoperative planning. The MRI is useful in assessing location of the fibroids in relation to the bladder, bowel, and pelvic sidewall. It can help differentiate between a submucosal versus intramural fibroid and can help assess the relationship of the fibroids to the endometrium – this can determine the best surgical approach. Intraoperatively, the surgeon can use the findings on the MRI to ensure that he or she has not left behind fibroids that may have otherwise gone undetected.

As a final tool, the MRI is also important in helping to better characterize a fibroid as benign or malignant. Sarcomas on MRI may show increased vascularity and increased enhancement with Gadolinium. This can be distinguished from degenerating fibroids, which have decreased

perfusion and enhancement. The results of the gadolinium-enhanced dynamic MRI, combined with results of LDH and LDH-3 isoenzyme, have been used to very accurately diagnose sarcoma in patients with uterine masses (Goto et al. 2002). In that study, the combined use of LDH and MRI revealed 100 % specificity, 100 % positive predictive value, and 100 % negative predictive value for assessing the presence of sarcoma. However, other studies have found lower predictive values.

2.2 Expectant Management

Fibroids are not precancerous tumors and are rarely a surgical emergency. The treatment of fibroids is geared toward improving quality of life, and as such there is a strong role for expectant management.

Women who opt for expectant management should be aware of what to anticipate in terms of growth and symptoms if their fibroids are left untreated.

In one prospective study looking at 72 reproductive-aged women, serial MRI results revealed a median growth rate of the fibroids of about 9 % over a 6 month interval (Peddada et al. 2008). Not all the fibroids grew at the same rate, even when examining multiple fibroids in the same patient. In that same study, the rate of fibroid growth after age 35 decreased with time in Caucasian women. Importantly, the rate of growth did not slow down for African American women.

Some data suggests that in older, premenopausal women, fibroids can spontaneously regress if left untreated. Estimating a rate of regression for an individual patient is difficult, however, as it appears to be most contingent upon patient age and race. Although not well documented, some evidence shows that fibroids regress following menopause (Ross et al. 1986).

As mentioned, "rapid uterine growth," is not suggestive of uterine cancer. Patients with sarcoma are usually older, and often present with abdominal and pelvic pain, vaginal bleeding, and worrisome imaging. In one analysis of the SEER database between 1989 and 1998, the average age of women diagnosed with sarcoma was about 63 years old. The average age of women undergoing myomectomy was 36 years old (Brooks et al. 2004; Parker et al. 1994). While there are currently no accurate screening tools for uterine sarcoma, a complete history, accompanied by appropriate labs and imaging, can help guide the clinician's suspicion for cancer and counsel the patient accordingly.

Women for whom expectant management would not be appropriate are those with symptomatic anemia due to excessive abnormal uterine bleeding, women who develop obstructive hydronephrosis due to ureteral compression, and women who develop venous compression with subsequent clot formation from fibroids.

2.3 Medical Management

2.3.1 NSAIDS

Currently, there is no data to suggest that NSAIDs decrease the amount of blood loss caused by fibroids. NSAIDs have also not been shown to affect fibroid size or pressure symptoms. While they may be helpful in the management of dysmenorrhea, NSAID therapy is not an appropriate treatment for women who present with abnormal uterine bleeding or pelvic pain secondary to fibroids. NSAID therapy is very effective in the management of women with pain from fibroid degeneration.

2.3.2 GnRH Therapy

Of the medical treatments available to women, GnRH agonists have been shown to be the most effective, short-term option. GnRH agonists function by causing an initial upregulation of gonadotropins, followed by a downregulation, inducing a temporary state of menopause. It is administered as an intramuscular injection and is available in two doses: 3.75 mg IM every month or 11.25 mg IM every 3 months. Data has shown that 6 months of treatment with GnRH agonists can improve heavy bleeding, reduce fibroid size by approximately 30 %, and decrease overall uterine volume by 35 % (Schlaff et al. 1989). This reduction in size is most appreciated in the first 3 months of

treatment, and a majority of women will have improvement in their bleeding profile by 6 months (Friedman et al. 1991).

The most common side effects of GnRH therapy include hot flushes, vaginal dryness, and frontal headaches. Other less common symptoms include loss of libido, arthralgias, myalgias, insomnia, emotional lability, edema, and depression. Treatment for longer than 6 months may be associated with loss of bone density. Addition of progestin therapy such as norethindrone may help improve symptoms without affecting the induced amenorrhea or fibroid shrinkage. While a majority of women will choose to remain on therapy for a short treatment course despite these symptoms, patients should be counseled on what to expect prior to initiation of treatment (Leather et al. 1993).

Peri-menopausal or late reproductive aged women may be most likely to benefit from this therapy. Initiation of GnRH agonist treatment can be used by providers to medically induce an earlier menopause in these patients until natural menopause occurs. Younger, reproductive-aged women who are further away from menopause are likely to re-develop their symptoms after discontinuation of treatment, often demonstrating rebound bleeding and fibroid growth. It is therefore not considered an effective long-term option for these patients. However, this therapy may be considered for either group of patients prior to surgical treatment to reduce fibroid size.

2.3.3 Levonorgestrel Intrauterine Device

Observational studies have shown that the levonorgestrel intrauterine device appears to be effective in management of abnormal uterine bleeding secondary to uterine fibroids. In one study, nearly 85 % of women with abnormal uterine bleeding secondary to fibroids developed a normal bleeding pattern after 3 months of treatment, and by 12 months approximately 40 % of women had amenorrhea (Grigorieva et al. 2003). Currently, the levonorgestrel intrauterine device is approved for the management of heavy menstrual bleeding.

Appropriate candidates for this treatment are thought to be women with fibroids <5 cm diameter and those with fibroids that are less than 50 % intracavitary (Soysal and Soysal 2005). The presence of intracavitary fibroids is considered a relative contraindication to placement of the device. Women with large, bulky fibroids that distort the endometrial cavity should be counseled that they may have a higher rate of expulsion due to distortion of the endometrial cavity.

2.3.4 Mifepristone

Other progestin treatment that has been evaluated includes progesterone antagonists. In one study, use of mifepristone was associated with an almost 50 % reduction in uterine size after 6 months (Steinauer et al. 2004). However, because mifepristone causes a state of unopposed estrogen, it can be associated with development of endometrial hyperplasia. In one systematic review of the effects of mifepristone on uterine fibroids, the rate of simple endometrial hyperplasia diagnosed by biopsy was 28 %. There were no cases of atypical hyperplasia. It is currently not considered standard medical treatment for management of symptomatic fibroids.

2.3.5 Ulipristal Acetate

Ulipristal acetate is a progesterone receptor modulator. Unlike mifepristone, it does not induce a state of unopposed estrogen and as such has little effect on serum estradiol levels.

European studies assessing the effects of preoperative ulipristal acetate treatment on women with heavy bleeding and uterine size less than or equal to 16 weeks demonstrated a significant reduction in bleeding after 3 months (Donnez et al. 2012). A 12–21 % reduction of uterine size was also noted. No hyperplasia was found in patients treated with the ulipristal.

Ulipristal acetate is not currently available in the United States at the same doses used in the above studies and as such is not used for the preoperative treatment of fibroids and bleeding.

2.4 Surgical Management

The surgical management of fibroid symptoms is broad and includes myomectomy, laparoscopic radiofrequency volumetric thermal ablation

(LRVTA), laparoscopic uterine artery occlusion, endometrial ablation, and hysterectomy. Preoperative history and examination, imaging, surgeon skill, and patient preferences will determine which option is best for each patient.

Appropriate preoperative planning is an essential component for intraoperative preparedness. For patients presenting with severe anemia secondary to heavy vaginal bleeding, preoperative correction of anemia is recommended. Depending upon the patient's level of acuity, iron supplementation can be given either orally or as an intravenous infusion. An intravenous infusion of iron 1000 mg is often sufficient to treat preoperative anemia and replete iron stores without causing overload. Hemoglobin levels start to rise in 2–3 weeks, and the deficit is usually halved after 1 month of treatment. Levels should return to normal within 6–8 weeks after treatment.

Recombinant erythropoietin can also be administered preoperatively for patients who present with significant anemia. Data from cardiac, orthopedic, and neurologic surgery has shown that administration of recombinant erythropoietin for 3 weeks prior to surgery can significantly increase hemoglobin rates and decrease the subsequent need for transfusion (Wurnig et al. 2001).

As mentioned in the Medical Management section of this chapter, GnRH agonists can also be used to improve preoperative hemoglobin and to decrease fibroid and uterine size. Data assessing the preoperative treatment of patients with iron and GnRH agonists demonstrated a significant improvement in hemoglobin levels after 3 months compared to women receiving only iron with a placebo (Stovall et al. 1995). Further data suggests that preoperative treatment with a GnRH agonist for 3–4 months prior to abdominal myomectomy can significantly reduce the amount of intraoperative blood loss (Lethaby et al. 2002).

2.4.1 Myomectomy

Surgical options for removal of fibroids within the uterus include abdominal, laparoscopic or robotic, and hysteroscopic myomectomies. Myomectomy is an appropriate option for women who desire uterine preservation and should be offered to patients who desire surgical management of their fibroids. One study comparing intraoperative risks of myomectomy versus hysterectomy found that while myomectomy was associated with longer operative times (200 vs. 175 min), there was a higher estimated blood loss in the hysterectomy group (484 vs. 227 mL) (Sawin et al. 2000). Performing a myomectomy largely avoids dissection of bladder and retroperitoneal structures and as such is considered a safe alternative to hysterectomy.

Medical techniques to decrease intraoperative blood loss may help the surgeon safely remove even very large fibroids. In one randomized controlled trial, misoprostol administered 2 h prior to surgery was shown to significantly decrease intraoperative blood loss (Kaligiannidis 2011). Use of perioperative tranexamic acid has also shown to reduce intraoperative blood loss by up to 40 % (Shaaban et al. 2015). Intraoperative use of vasopressin, an anti-diuretic hormone, via injection into the fibroid pseudocapsule can also be used to decrease intraoperative blood loss during myomectomy (Frederick et al. 1994). Mechanical constriction of the uterine arteries, ovarian vessels, and utero-ovarian ligaments via tourniquets and clamps may also decrease the amount of blood loss during the myomectomy.

Another method used to decrease need for heterologous blood transfusion is employment of a cell- saver device. By suctioning blood from the operative field and storing the blood with heparin and saline in a canister, this blood can be returned to the patient if they require intraoperative transfusion. Returning the patient's own blood reduces the risk of transfusion reaction and infection (Yamada et al. 1997).

Regardless of the route of myomectomy, patients should be counseled on the risk of development of new fibroids after surgery. It is estimated that if a woman only has one fibroid present at the time of surgery, her risk of requiring a repeat surgery for a new appearance of fibroids is approximately 11 % (Malone et al. 1969). If a woman has multiple fibroids at the time of her surgery, her risk of requiring a repeat surgery for a new appearance is approximately 26 %. This data is important to review with patients, as they may opt for definitive management via hysterectomy

instead of myomectomy if they are concerned about the possibility of repeat surgery.

Abdominal Myomectomy

Appropriate candidates for an abdominal myomectomy can include patients with numerous very large fibroids, patients in whom the fibroids are palpated to be heavily resting on the pelvic sidewall, and patients who desire fertility with fibroids that are largely abutting the endometrium.

The uterine incisions made during a myomectomy can be either vertical or horizontal, as neither direction has been found to decrease the amount of blood loss during the procedure. Planning of the location of the incisions is important, as unanticipated extension of incisions into the cornua could lead to distortion of anatomy.

Post-operative recovery time following laparotomy is longer than with minimally invasive surgery. Patients should plan to spend 2–3 nights in the hospital. Pain control can be accomplished through intravenous narcotics, oral narcotics, NSAIDs, and continuous infusion of bupivacaine at the incision site via an elastomeric pump. Early ambulation, early introduction of regular diet, and decreased amount of time with a urine catheter can help the patient have a normal recovery and reduce complications such as deep venous thrombosis and urinary tract infections.

Laparoscopic and Robotic Myomectomy

Patients with numerous, large fibroids may also be candidates for laparoscopic myomectomy. The size and location of the fibroids, the patient's fertility goals, and the surgeon's level of skill with laparoscopic suturing should determine whether the fibroids can be safely removed laparoscopically. Patients desiring fertility with fibroids abutting the endometrium can also have a laparoscopic myomectomy; however, decreased haptic feedback during laparoscopy may increase the possibility of endometrial damage.

Removal of fibroids from the abdominal cavity in a laparoscopic myomectomy requires morcellation of the specimen. Morcellation can be accomplished via manual morcellation at one of the trocar sites, extension of a laparoscopic incision and manual morcellation via this incision, and power morcellation. Power morcellation involves the use of a specialized, circular blade that cuts the specimen into small pieces for removal via a small laparoscopic incision. All of these methods can employ the use of an endoscopic bag, into which smaller pieces of the fibroid may fall.

The use of laparoscopic power morcellation has recently been brought to question by the United States Food and Drug Administration (FDA). Based upon a case report of a poor outcome for a patient who underwent laparoscopic power morcellation of an undiagnosed sarcoma, the FDA initiated an investigation of the incidence of sarcoma in women undergoing this procedure. A limited literature review conducted by the FDA revealed that for every 458 women having surgery for presumed fibroids, one will have an unsuspected leiomyosarcoma (FDA Safety Communication). Subsequent studies have revealed much lower estimates, showing that the prevalence of leiomyosarcoma among women undergoing surgery was 1 in 1960 (Pritts et al. 2015). A study conducted to evaluate the effects of the FDA warning on surgical practice and patient outcomes demonstrated a significant decrease in laparoscopic hysterectomy with subsequent increase in vaginal and abdominal hysterectomy in the first 8 months after the FDA warning, with subsequent increase in surgical complication rates (Harris et al. 2016). Clinicians should complete a thorough preoperative evaluation of all women who may undergo laparoscopic fibroid removal, and the patient should specifically be consented for the use of power morcellation.

Hysteroscopic Myomectomy

Patients with suspected intracavitary or submucous fibroids should be evaluated for hysteroscopic myomectomy. Success and safety of the procedure is determined by assessing the type of submucous fibroid, using Federation of Gynecology and Obstetrics (FIGO) classification system. Class 0 fibroids are defined as being entirely in the endometrial cavity. Class I fibroids extend less than 50 % into the myometrium. Class II fibroids extend greater than 50 % into the myometrium (Munro et al. 2011). Patients with

Type 0 and Type I submucosal fibroids can be appropriate candidates for hysteroscopic resection.

There is no established fibroid size cut off for performing hysteroscopic myomectomy. However, patients are more likely to have successful removal of the entire fibroid in one procedure if the fibroid is less than 3 cm (Hart et al. 1999). Larger fibroids can be removed via hysteroscopy; however, the patient should be counseled that it could require two procedures if rising fluid deficits do not allow enough time for complete removal.

Vasopressin can also be used during a hysteroscopic myomectomy to decrease blood loss. For a hysteroscopic myomectomy, the vasopressin is injected into the cervical stroma, which can cause significant reduction in intraoperative blood loss (Wong et al. 2014). Care should be taken to avoid intravascular injection as this has been reported to cause hypertension, bradycardia, and morbidity.

Risks of hysteroscopy include excessive intravascular absorption of distension media, which can cause electrolyte imbalances, pulmonary edema, cerebral edema, cardiac failure, and even death. It is generally recommended to terminate a hysteroscopic procedure once the fluid deficit reaches 1500 mL of a nonelectrolyte distention media or 2000 mL of an electrolyte-positive distension media (Loffer et al. 2000). For this reason, it can be more difficult to remove larger fibroids >4 cm in one procedure, as this is often associated with longer operative time, more intravascular absorption of fluid through the exposed myometrial bed, and subsequent higher risk of excessive fluid deficit.

2.4.2 Laparoscopic Radiofrequency Volumetric Thermal Ablation (LRVTA)

More recent technology for the minimally invasive management of fibroids includes the use of laparoscopic radiofrequency volumetric thermal ablation (LRVTA). In this procedure, a laparoscopic ultrasound transducer is introduced into the abdomen via a trocar to map out the location of fibroids. A radiofrequency hand piece containing a seven-needle electrode is also introduced and using the ultrasound transducer to locate the exact position of the fibroids, the hand-piece deploys the electrodes into the fibroid to deliver a continuous, alternating current (Chudnoff et al. 2013). LRVTA candidates include women who are pre-menopausal, with 6 or fewer fibroids, none of which exceeds 7 cm, who have heavy menstrual bleeding, who have completed child bearing, and who do not have an active coagulopathy. In addition, patients should be counseled that the results are not immediate – as such, good candidates also include women who are amenable to waiting months to years to see results. Inappropriate candidates include women with adenomyosis as seen on MRI, women with pedunculated or submucosal fibroids, and women with a history of gynecologic cancers or who may have cervical dysplasia.

Data looking at changes in bleeding pattern as well as fibroid size in 135 women who underwent the procedure have demonstrated an improvement in menstrual blood loss and a decrease in fibroid size by approximately 45 % as measured on MRI (Berman et al. 2014). This group included only women with fibroids no greater than 7 cm. When re-evaluated in 3 years, the same cohort of women still experienced improvement in quality of life, while 11 % required a repeat intervention.

Women who elect to undergo this procedure can expect to go home on the same day of surgery. Risks of the procedure include postoperative pelvic abscess, bowel injury, post procedure vaginal bleeding, and pain (Chudnoff et al. 2013).

2.4.3 Laparoscopic Cryomyolysis

Laparoscopic cryomyolysis is a less frequently used technique of also reducing fibroid size and subsequent symptoms. The technique was originally developed in 1996 and has subsequently been modified. It involved laparoscopic introduction of a cryoprobe into a fibroid to freeze the tissue.

Different studies have been inconsistent in demonstrating fibroid shrinkage and symptom improvement. More recent data analyzing 20 women who underwent the procedure without receiving preoperative GnRH agonist shows an

average fibroid shrinkage of 62 % at 12 months after surgery (Zupi et al. 2005). The majority of patients in this study reported being strongly satisfied with the improvement in their symptoms.

Appropriate candidates for this procedure are women over 40 years old, with fibroids between 4 and 8 cm in diameter, who do not desire future fertility. Patients who are undergoing this procedure should be counseled that it may cause an increased risk of pelvic adhesive disease. In one study, 53 % of women undergoing laparoscopy for other reasons following their cryomyolsis were found to have dense pelvic adhesions (Donnez et al. 2000).

2.4.4 Uterine Artery Occlusion

Apart from uterine artery embolization, which will be discussed later on in this chapter, surgical occlusion of the uterine arteries has also been described via laparoscopic approach. This approach is not commonly performed, and there is paucity of robust data to describe standard technique, demonstrate effectiveness of treatment, and establish patient safety.

In laparoscopic uterine artery occlusion, the retroperitoneum is entered, and the uterine artery is dissected and isolated. It is then either clamped or coagulated. Case series publications demonstrate short operating times (30.8 min average) and a low complication rate (7.3 %) (Holub et al. 2004). In these series, women followed at 12 months after their procedures demonstrated a 57.8 % reduction in fibroid size.

2.4.5 Endometrial Ablation

Ablation of the endometrial cavity, with or without concurrent resection of submucosal fibroids, may also be used as a surgical management option for women with fibroids. There are currently five devices approved by the Food and Drug Administration to be used for endometrial ablation. These include devices that use a thermal balloon in the endometrial cavity, devices that circulate very hot fluid inside the cavity, radiofrequency electrosurgery, cryotherapy, and microwave energy. In one study looking at the amount of bleeding reported after hysteroscopic endometrial ablation, 94 % of women who had undergone an ablation with or without resection of fibroids reported improvement in their bleeding patterns at the end of 2 years (Indman 1993).

Appropriate candidates for endometrial ablation include women who can tolerate hysteroscopy in general, women with heavy menstrual bleeding or abnormal uterine bleeding thought to be secondary to fibroids, women who do not have submucous fibroids, women who do not have any suspected endometrial cancers, and those who do not desire future fertility.

The rate of injury with endometrial ablation is low and varies depending upon which device is used. These injuries include genital tract burns, bowel injury, uterine perforation, infection, uterine and cervical scarring, hemorrhage, ureteral thermal damage, and ureterovaginal fistulas (Gurtcheff and Sharp 2003).

2.4.6 Hysterectomy

Hysterectomy is the definitive management for women with fibroids, and as such fibroids represent the most common indication for hysterectomy. It is estimated that fibroids account for 30 % of hysterectomies in white women and 50 % of hysterectomies in black women (Management of Uterine Fibroids 2001). The procedure can be performed abdominally, laparoscopically or robotically, or vaginally depending upon patient symptoms, the surgical history, the size of the uterus, and patient preference.

Women who have completed child bearing, who desire definitive treatment, and who no longer desire to keep their uterus are good candidates for a hysterectomy. However, women who are undergoing a hysterectomy should be counseled regarding the potential risks, including changes in hormone profile, as a hysterectomy has been associated with an increased risk of premature ovarian insufficiency as well as earlier onset of menopause (Moorman 2011).

2.5 Radiologic Management

2.5.1 Uterine Artery Embolization (UAE)

Uterine artery embolization (UAE) provides a minimally invasive method of reducing fibroid

size and symptoms while avoiding surgery. Patients should be evaluated both by an interventional radiologist as well as a gynecologist to assess candidacy for the procedure. Those who are good candidates for UAE are women with multiple fibroids but do not desire hysterectomy, women who are done with childbearing, women who do not have adenomyosis, women who are not taking GnRH agonists, and women who have not had previous ligation of the internal iliac artery.

During this procedure, interventional radiologists guide a catheter through the femoral artery and inject either gelatin sponges, polyvinyl alcohol particles, or tris-acryl gelatin microspheres into the uterine artery and its branches. The decreased tissue perfusion over time causes fibroids to shrink, with subsequent improvement in symptoms.

Women undergoing a UAE should be observed in the hospital for the first evening after their procedure, as it can be associated with severe pain. Most women require NSAIDs for the first 1–2 weeks following the procedure.

Data has shown that over the course of 3 months, a mean fibroid size reduction of about 33 % can be expected. In addition, almost 83 % of women will have improvement in their heavy menstrual bleeding, while 77 % should also have improvement in dysmenorrhea (Pron 2003). This procedure is also associated with a short recovery and hospital stay. Women who undergo UAE have a 9 % risk of need for repeat UAE or surgical intervention for fibroids (Edwards et al. 2007).

Because there are limited data observing the relationship between UAE and future fertility, it is not recommended for women who desire fertility. The relationship between UAE and subsequent ovarian function is also unclear. Data looking at ovarian perfusion via Doppler ultrasound following a UAE suggests that 35 % of women had decreased perfusion and up to 54 % had complete lack of perfusion (Ryu et al. 2001). Other data have shown a 45 % risk of ovarian failure in women over 45 years old after the procedure (Chrisman et al. 2000). There is insufficient data to determine whether UAE is associated with premature ovarian insufficiency.

2.5.2 MRI-Guided Focused Ultrasound (MRgFUS)

MRI-guided focused ultrasound (MRgFUS) utilizes high frequency ultrasound waves focused on fibroids as mapped on MRI. The ultrasound waves stimulate protein denaturation and coagulative necrosis of the fibroids. The MRI helps to focus the ultrasound and map out the location of organs to be avoided. The procedure itself takes approximately 2–4 h.

Data from patients who have undergone this procedure show that approximately 71 % of patients will reach their target symptom reduction at 6 months, while 51 % will reach this target at 12 months (Hindley et al. 2004; Stewart et al. 2006). By the end of 1 year, 21 % of patients required an additional, alternative treatment of their fibroids.

Benefits of this procedure are that it can reduce fibroid size without requiring laparoscopic surgery or invasive catheter placement. The procedure can be performed under conscious sedation, and recovery is immediate.

3 Conclusion

Fibroids are the most common benign tumors of the female reproductive tract. The majority of women with fibroids will be asymptomatic; however, among women who are symptomatic the most common complaints are heavy menstrual bleeding, infertility, and pelvic pressure.

The presence of fibroids rarely constitutes a surgical emergency. Therefore, clinicians should take the time to appropriately assess the patient's symptoms, fibroid location, and personal goals when developing treatment plans.

The management of fibroids is very broad. For those patients who are asymptomatic or who are satisfied with their level of symptoms, expectant management is a reasonable option. Fibroids do not have the potential to become cancerous. As such, clinicians should not feel obligated to treat fibroids to mitigate oncogenic potential. Medical management is a reasonable next step for patients who desire intervention with their symptoms. Effective medical options include the short-term

use of GnRH agonists for fibroid size reduction and improved bleeding profile, as well as the use of the levonorgestrel intrauterine device.

Women who desire intervention and are willing to wait several months to see an improvement in their symptoms may be good candidates for ablative and vascular occlusive procedures, including LRVTA, laparoscopic cryomyolysis, uterine artery embolization, and MRgHFU. Other options also include endometrial ablation, which has also been shown to be successful in reducing heavy menstrual bleeding associated with fibroids.

Other options for patients who desire surgical intervention include myomectomy, which can be accomplished through several different routes depending upon the number and location of fibroids, patient symptoms, and patient preferences. While this is not a definitive management of fibroids, it is an acceptable option for women seeking to preserve their uterus or maintain fertility. The risk of appearance of new fibroids is generally low, and the majority of women will not require re-operation for their fibroids after their first procedure.

The final option in the management of fibroids is a hysterectomy, which is the only definitive option available. Fibroids are the most common indication for performance of a hysterectomy. Women who undergo hysterectomy for their fibroids should be counseled that while it is a definitive treatment option, it could be associated with adverse changes in reproductive hormone profile.

Treatment of fibroids represents a unique opportunity for clinicians to tailor treatments specific to patient symptoms and goals. By offering patients a range of treatment options, the clinician has the opportunity to safely care for these patients and significantly improve their quality of life.

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Management of Abnormal Uterine Bleeding: Later Reproductive Years

Yoko Takashima, Janet Bruno-Gaston, and Jennifer Israel

Abstract

Abnormal uterine bleeding (AUB) is defined as bleeding outside of normal volume, duration, regularity, or frequency. AUB accounts for approximately one third of visits to a gynecologist. The estimated annual prevalence rate in US women, age 18–50 years, is 53 per 1,000 women (Kjerulff et al., Am J Public Health 86:195, 1996a). AUB can negatively impact a woman's quality of life, productivity, and reproductive potential.

Keywords

Abnormal uterine bleeding • Adenomyosis • Leiomyoma • Fibroids • Hyperplasia • Neoplasia • Ovulatory dysfunction • FIGO

Contents

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1 Introduction

Although leiomyomas are a common cause of AUB, not all bleeding is caused by leiomyomas. In fact, the majority of leiomyomas are asymptomatic. Therefore, other causes of AUB must be considered and ruled out. This chapter will address the guidelines for evaluation and treatment of reproductive-aged women with AUB that is unrelated to pregnancy.

A new classification system was proposed in 2011 by the International Federation of Gynecology and Obstetrics (FIGO) in an effort to create a universally accepted system of nomenclature (Munro et al. 2006). The acronym **PALM-COEIN** (**P**olyp, **A**denomyosis, **L**eiomyoma, **M**alignancy-**C**oagulopathy, **O**vulatory dysfunction, **E**ndometrial, **I**atrogenic, **N**ot yet classified) has been adopted to standardize terminology to describe the etiology of AUB (Munro et al. 2011).

2 Structural (PALM)

2.1 Polyp

2.1.1 Clinical Manifestations

Endometrial and endocervical polyps are a common cause of AUB (Kjerfulff et al. 1996a), both in premenopausal and postmenopausal women. The reported prevalence ranges from 7.8% to 34.9% and are more common in postmenopausal women (Munro et al. 2011). They are comprised of overgrowths of vascular, glandular, and connective tissue that project from the surface of the endometrium and can be sessile or pedunculated in nature. Many times they are asymptomatic and found incidentally during routine pelvic examination, Pap smear, endometrial biopsy, pelvic imaging, hysteroscopy, or work-up for infertility. Risk factors associated with polyp formation and growth include obesity, hypertension, and tamoxifen use. The most common presentation is vaginal bleeding and patients often complain of intermenstrual bleeding. Polyps are also found in 12–25% of infertile women (Salim et al. 2011). They are usually benign, however can have hyperplastic features with malignant transformation. The incidence of hyperplasia without atypia is 11.4%. The incidence of atypia and carcinoma is seen in as high as 4.8% with risk factors for malignancy including age, postmenopausal status (Oguz et al. 2005), endometrial thickness >1.5 cm, history of hypertension, and tamoxifen use (Di Spiezio et al. 2015; Lieng et al. 2010; Ben-Arie et al. 2004).

2.1.2 Diagnostics

Transvaginal ultrasound (TVUS) is the first-line imaging modality for patients with AUB (American College of Ob/Gyn 2012). Polyps are typically hyperechoic lesions with regular contours within the endometrial cavity surrounded by a thin hyperechoic halo (Martinez-Perez et al. 2003). These findings are not specific to polyps and can be seen in other uterine abnormalities, like submucosal myomas. To further characterize the polyp or for patients with uncertain ultrasound findings, a saline infusion sonogram (SIS) (ACOG 2012) or diagnostic hysteroscopy is recommended. SIS increases sonographic contrast of the uterine cavity to better evaluate the polyp and its features. SIS also allows detection of smaller lesions that were unable to be visualized on TVUS. Hysteroscopy with guided biopsy is the gold standard for the diagnosis of uterine polyps. It gives the ability to both directly visualize and to biopsy or remove the lesion. Other diagnostic methods that are less commonly utilized are blind dilation and curettage (D&C) for pathological diagnosis, hysterosalpingography (HSG), and pelvic MRI. If fertility is being evaluated, HSG is a good option to evaluate both the endometrial cavity and fallopian tubes. Three-dimensional ultrasound (3D US) is a noninvasive imaging technique with the ability to generate multiplanar reconstructed images through the uterus. 3D US allows the uterus to be visualized in coronal view, which allows for superior diagnostic accuracy (Ahmad et al. 2011).

2.1.3 Treatment

Conservative medical management is an option, though the efficacy compared to low-risk surgical procedures, the cost-effectiveness, and the risk/benefit ratio must be considered. GnRH agonists have been shown to give short-term relief from polyps though symptom recurrence is common (Vercellini et al. 1994). Combined hormone replacement therapies and levonorgestrel-releasing intrauterine system (LNG-IUS) have also been studied with limited data (Lieng et al. 2010; Gardner et al. 2009). Conservative surgical management, including blind D&C and TVUS-guided polypectomy, has been commonly used but not recommended. However, given low risk of hysteroscopic resection, hysteroscopic methods are preferred (Munro et al. 2011). The most effective and safe method of diagnosis and treatment of endometrial polyps is hysteroscopy and polypectomy. The polypectomy can be performed via polyp forceps, polyp morcellation, or removal via electroloop. Recurrence rate is low, about 3.7%, and only 1.7% of patients undergoing hysteroscopic resection required repeat hysteroscopic resection (Preutthipan and Herabutya 2005). The most aggressive management option

is a hysterectomy for definitive treatment. It is the treatment of choice for polyps associated with malignancy or neoplasia.

2.2 Adenomyosis

2.2.1 Clinical Manifestations

Adenomyosis is a condition in which the endometrial glands and stroma are located haphazardly within the myometrium (Reinhold et al. 1999). The ectopic endometrial proliferation within the myometrium causes reactive changes, including smooth muscle cell hyperplasia and hypertrophy, leading to a diffusely enlarged uterus (Ferenczy 1998). Adenomyosis is most frequently seen in parous women in their mid to late 40s (Azziz 1989). The prevalence ranges from 5% to 70%, likely due to inconsistent diagnostic criteria (McElin and Bird 1974). The relationship between adenomyosis and AUB is unclear. Adenomyosis is asymptomatic in up to half of all cases, but patients can present with various symptoms including AUB, dysmenorrhea, dyspareunia, and chronic pelvic pain.

2.2.2 Diagnostics

Definitive diagnosis is made by histopathological examination of a uterine specimen; however, TVUS and magnetic resonance imaging (MRI) have been frequently used for accurate, noninvasive diagnosis. Adenomyosis may also be incidentally noted on hysterosalpingogram in patients undergoing fertility evaluation. The sensitivity and specificity for TVUS are 72% and 81%, respectively, while the sensitivity and specificity for MRI are 77% and 89%, respectively (Champaneria et al. 2010). The characteristics seen in adenomyosis on both imaging modalities are increased heterogeneity of the myometrium, linear striations radiating from the endometrium, myometrial cysts, poor definition of the endomyometrial junction, poor definition of lesion borders, and elliptical myometrial abnormality (Reinhold et al. 1999).

2.2.3 Treatment

Hysterectomy is the definitive treatment for adenomyosis. There is limited data on the efficacy of conservative management in adenomyosis. Though studies are limited, combined oral contraceptives, danazol, and GnRH agonists, commonly used in treatment for dysmenorrhea and endometriosis, can be used (Kitawaki 2006). The LNG-IUD has been studied in adenomyosis, showing reduction in pain and AUB, as well as reduction in junctional zone thickness on MRI. The overall satisfaction after 36 months with the LNG-IUS for management of dysmenorrhea was 72.5% (Fedele et al. 1997; Bragheto et al. 2007; Sheng et al. 2009). Long-term follow-up for management of AUB has not been studied. Uterine artery embolization (UAE) has been shown to be successful in reduction in uterine size and improvement in dysmenorrhea and AUB. 57.4% of women had success at long-term follow-up at 3 years or longer and a mean reduction in uterine volume of 27.4% at long-term follow-up. Seventy percent of women were satisfied at their long-term follow-up even with a symptom recurrence rate of 38% (Kim et al. 2007).

2.3 Leiomyoma

2.3.1 Clinical Manifestations

Uterine leiomyomata are the most common gynecologic tumor in women and the leading cause of hysterectomy in the United States. The incidence of fibroids has been shown to be as high as >80% in African-American women and almost 70% in white women (Baird et al. 2003). African-American women are diagnosed at a younger age compared to Caucasian women, 37.5 years versus 41.6 years. African-American women were also found to have a greater number of leiomyomas, higher incidence of anemia, and more likely to report severe pelvic pain (Kjerulff et al. 1996b). Other risk factors include increasing parity, early menarche, and use of oral contraceptives before 16 years of age (Stewart 2015; Marshall et al. 1998). Symptomatology varies based on size, number, and location of fibroids. The

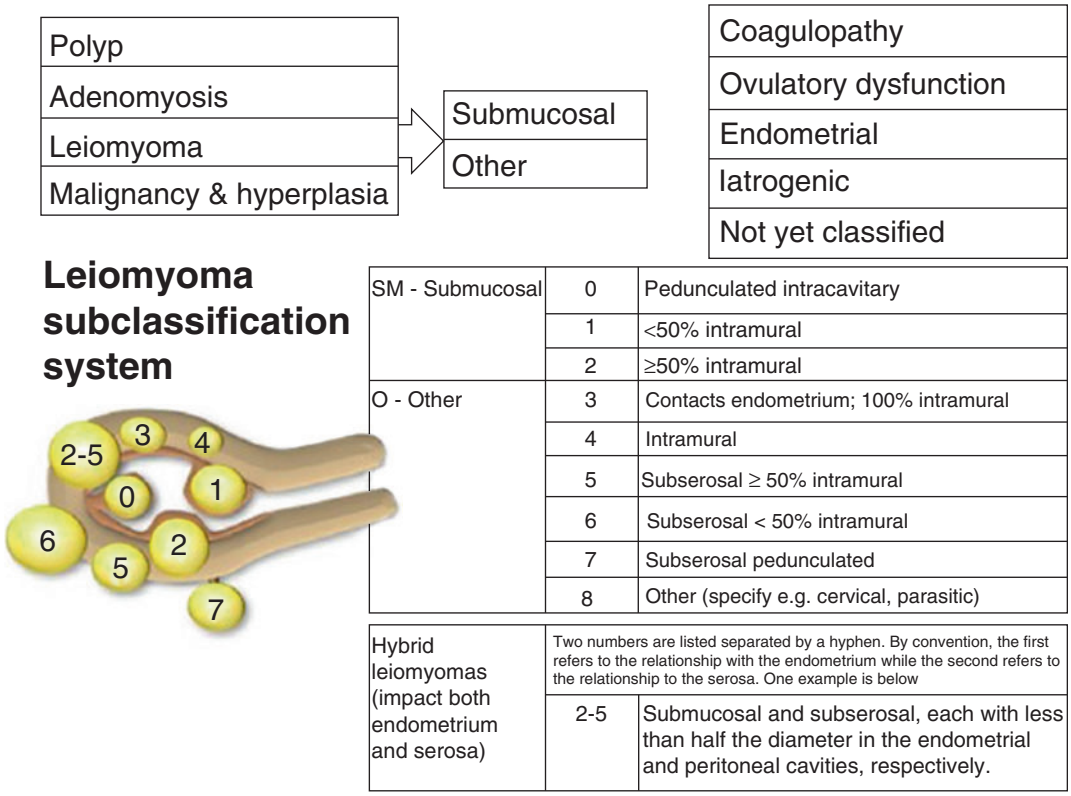

Fig. 1 FIGO leiomyoma subclassification system

FIGO classification system is used to describe fibroid location (Fig. 1) (Munro et al. 2011).

Uterine myomas can be asymptomatic or present with one or more of the three common manifestations: AUB, pelvic pain and pressure, and reproductive dysfunction. AUB is the most common symptom of fibroids and can cause heavy or prolonged menstrual periods. In particular, submucosal fibroids, which protrude into the uterine cavity, were found to be associated with higher risk of anemia (Puri et al. 2014). Patients can also complain of dysmenorrhea, dyspareunia, abdominal protrusion, and bulk-related symptoms, including bowel and bladder dysfunction. Infertility and recurrent miscarriages can also be seen. There has been a significant debate regarding prevalence of undiagnosed uterine malignancy given the use power morcellation in minimally invasive surgeries for gynecologic surgeries and potential spread. The prevalence in a large cohort study of women who underwent minimally invasive hysterectomy was found to be 27/10,000 and was found to increase with increasing age (Wright et al. 2014).

2.3.2 Diagnostics

Diagnosis of leiomyomas is usually suspected with a history of AUB and/or enlarged uterus or pelvic mass on physical examination. The imaging modality used to confirm this diagnosis is ultrasonography. A SIS can also be performed to identify the extent of the intracavitary fibroids. MRI with contrast can also be used to further characterize fibroids and help with surgical planning and may help facilitate a minimally invasive approach. MRI has also been used for suspected leiomyosarcomas, and though there are some characteristics that are suggestive for malignancy, it cannot be used to definitively rule out sarcomas (Tanaka et al. 2004).

2.3.3 Treatment

There are various treatment options for leiomyomatous uteri. Expectant management can be used for asymptomatic fibroids or in patients who decline both surgical and medical management. Medical therapy is frequently used for symptomatic relief, particularly when AUB is the dominant symptom. Medical management offers effective short-term relief, but many patients will later undergo surgery (nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in management of dysmenorrhea). Contraceptive steroids (estrogen and progestin combinations and progestin alone) are widely used, and often the first-line treatment, for control of AUB. LNG-IUS provides beneficial local effect for improvement in AUB when used in the appropriate candidate and has been shown to be equally as effective compared to surgery in improvement in quality of life (ACOG Practice Bulletin No. 96 2008; Marjoribanks et al. 2006; Olive et al. 2004). GnRH agonists have also been used and have been shown to reduce uterine volume by 35–65% within 3 months. If treatment lasts for more than 6 months, add-back steroidal therapy should be considered. Other less commonly used options include aromatase inhibitors and progesterone modulators, such as mifepristone or raloxifene. For patients who desire uterine preservation, myomectomy is an option, which can be done either hysteroscopically, laparoscopically, or open. Uterine artery embolization is also an option for patients who desire to avoid surgery. Although 28.4% of patients with a UAE required a secondary hysterectomy in the first 5 years, 82.7% of patients were symptom-free or reported improvement of symptoms, and 85.3% were satisfied with their treatment, compared to 88.6% of women who received a hysterectomy (Hehenkamp et al. 2006). Definitive management for uterine fibroids is hysterectomy, which can be performed vaginally, laparoscopically, or open. Please refer to the chapter on "▶ Management of Uterine Fibroids."

2.4 Malignancy

2.4.1 Clinical Manifestations

Risk factors for endometrial neoplasia include older age and unopposed estrogen, such as chronic anovulation, estrogen secreting tumors, and excessive peripheral conversion of androgens to estrone in adipose tissue in obese patients. Other risk factors include white race, nulliparity, late age at natural menopause, early age at menarche, tamoxifen use, Lynch syndrome, and history of type 2 diabetes or hypertension (ACOG Practice Bulletin No. 65 2005).

Endometrial hyperplasia is defined as abnormal proliferation of the uterine endometrial glands resulting in a greater gland-to-stroma ratio. Women with endometrial hyperplasia have an elevated risk of endometrial carcinoma (Kurman et al. 1985; Trimble et al. 2006). AUB, particularly postmenopausal vaginal bleeding, is a cardinal symptom of endometrial malignancy. Patients with advanced disease can present with abdominal or pelvic pain, abdominal distention, bloating, early satiety, or change in bowel or bladder function. Endometrial hyperplasia is commonly classified using the WHO classification based on the glandular/stromal pattern, simple versus complex, and presence or absence of nuclear atypia. The risk of progression to endometrial carcinoma, based primarily on the presence of atypia, is 1% for simple hyperplasia without atypia, 3% for complex hyperplasia without atypia, 8% for simple atypical hyperplasia, and 29% for complex atypical hyperplasia. Atypical hyperplasia is also known as endometrial intraepithelial neoplasia by other classification systems. On final pathology of patients who underwent hysterectomy for atypical endometrial hyperplasia, 42.6% of women were found to have invasive cancer (Trimble et al. 2006). For FIGO staging of endometrial carcinoma, refer to the chapter on "▶ Gynecologic Oncology."

2.4.2 Diagnostics

Patients who present with symptoms concerning for endometrial malignancy should be evaluated with physical examination, pelvic ultrasound to measure endometrial thickness, and histological

evaluation via endometrial biopsy or curettage sample. When transvaginal ultrasound is used and the endometrial thickness is less than or equal to 4 mm, endometrial sampling is not required (ACOG Committee Opinion No. 440 2009). The specificity of endometrial sampling with disposable pipelle is 98% (Dijkhuizen et al. 2000). It has been suggested that a follow-up D&C should be performed after initial endometrial biopsy. Although the risk of unexpected endometrial carcinoma was lower for patients who had single preoperative sampling with D&C versus endometrial biopsy (30% vs. 45%), D&C cannot be reliably used preoperatively to exclude cancer in patients with complex endometrial hyperplasia with atypia (Suh-Burgmann et al. 2009). Refer to the chapter on "▶ Gynecologic Oncology" for treatment if endometrial carcinoma is diagnosed.

2.4.3 Treatment

Generally, treatment for endometrial hyperplasia is progestin-based therapy. Approximately 70% of women with complex hyperplasia without atypia had regression of their lesion whether or not they were treated. Only 33.3% of women with atypical hyperplasia had regression without treatment, compared to 73.1% regression with progestin treatment (Reed et al. 2009). Oral progestins, including norethisterone acetate, megestrol acetate, and medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine system (LNG-IUS) are nonsurgical options (Table 1). The LNG-IUS achieved better therapeutic response rate and hysterectomy rates compared to oral progestins and should be offered as an alternative to oral progestins (Abu et al. 2015). Hysterectomy is the preferred treatment in most women with endometrial hyperplasia with atypia who are no longer interested in childbearing. Although there is no consensus regarding surveillance with medical therapy, generally endometrial sampling every 3–6 months is considered acceptable.

Table 1 Hormonal treatment for endometrial intraepithelial neoplasia/atypical hyperplasia (ACOG Committee Opinion No. 631 2015)

Medication	Dosage
Medroxyprogesterone acetate	10–20 mg/d or cyclic 12–14 days per month
Depot medroxyprogesterone	150 mg intramuscularly, every 3 months
Micronized vaginal progesterone	100–200 mg/d or cyclic 12–14 days per month
Megestrol acetate	40–200 mg/d
Levonorgestrel intrauterine system	52 mg in a steroid reservoir over 5 years

3 Nonstructural (COEIN)

3.1 Coagulopathy

3.1.1 Clinical Manifestations

Coagulopathy refers to an array of bleeding disorders in which the body's ability to form clots has been compromised. Interruptions in the clotting cascade can result in excessive bleeding and/or catastrophic hemorrhage. Primary coagulopathy results from intrinsic defects in the clotting cascade, while secondary coagulopathy results as a complication of other systemic disorders, trauma, or iatrogenic. Studies have shown that approximately 13% of women with heavy menstrual bleeding have some underlying bleeding disorder, von Willebrand disease being the most common (Shankar et al. 2004). The extent to which they contribute to, or are solely responsible for heavy menstrual bleeding, is yet to be determined. However, clinicians should proceed with a hematologic evaluation when clinically plausible and other likely etiologies have been excluded.

Patients with underlying coagulopathy have a wide range of clinical presentations, and evaluation must begin with identifying primary or secondary disorders of hemostasis (Fig. 2). Women with primary coagulopathy may report normal cycle lengths with prolonged heavy menses since menarche. They may also report bleeding complications outside of menses including epistaxis, excessive bleeding with dental procedures, and easy bruising. The clinical presentation for secondary coagulopathy is much less specific and depends on the underlying systemic disorder or inciting event.

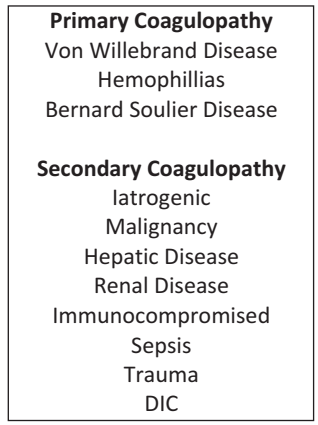

Fig. 2 Primary and secondary disorders of hemostasis

3.1.2 Diagnostics

The evaluation should begin with a thorough history and physical examination with efforts made to illicit any hereditary bleeding disorders or acquired coagulopathy due to underlying medical condition or medication. Pelvic ultrasound is usually sufficient to exclude structural causes, but further imaging may be warranted if findings are unclear. Laboratory investigations should include CBC, bleeding time, and coagulation panel with inclusion of specific assays like the vWBF ristocetin cofactor assay when primary coagulopathy is suspected.

3.1.3 Treatment

The complexity of bleeding disorders requires a multidisciplinary approach to treatment and long-term management. Referrals and routine follow-up with hematology should be initiated upon discovery of a primary bleeding disorder. The acuity of bleeding should be assessed and appropriate resuscitation with blood products initiated if indicated. Patients with primary and secondary coagulopathy from chronic anticoagulation should be managed in conjunction with the hematologist although most patients can be tried on medical regimens if there are no clear contraindications. Antifibrinolytic therapy such as tranexamic acid and estrogen-based therapy such as oral contraceptives can be considered as long as the patient has primary coagulopathy or is not undergoing treatment for an active thrombus or prophylaxis for thrombophilia (Table 2). Persistent anemia and/or intolerable bleeding profile or medication side effects may warrant consideration of surgical treatment options. Surgical management may range from minimally invasive options like endometrial ablation without or with GnRH pretreatment (Vercellini et al. 1994), uterine artery embolization, or minimally invasive hysterectomy (Kadir et al. 2005; Lethaby et al. 2000).

Table 2 Treatments for AUB-C (Kadir et al. 2005; Lethaby et al. 2000)

Treatment	Dosage
Tranexamic acid	1,300 mg PO TID × 5 days
Combined oral contraceptive pills	Monophasic combined oral contraceptive that contains 30–35 micrograms of ethinyl estradiol
Desmopressin acetate	Intranasal 1 puff to each nostril for the first 2–3 days of menses, with or without tranexamic acid
LNG-IUD	52 mg levonorgestrel intrauterine device

3.2 Ovulatory Dysfunction

3.2.1 Clinical Manifestations

The menstrual cycle represents a tightly controlled sequence of hormonal signals between the brain, ovaries, and uterus (Fig. 3). Hormonal derangements anywhere along hypothalamic-pituitary-ovarian axis can result in anovulation and subsequent abnormal uterine bleeding. The corpus luteum is a transient endocrine organ that normally develops from the ruptured follicle following ovulation. It secretes progesterone that acts on the endometrium by promoting secretory changes and decidualization. If implantation occurs and the pregnancy continues to develop, the corpus luteum will continue to support the endometrium. If not it will regress and menses ensues. In the absence of ovulation, the corpus luteum fails to develop, and the ovary fails to secrete progesterone. This leaves the endometrium exposed to unopposed estrogen resulting

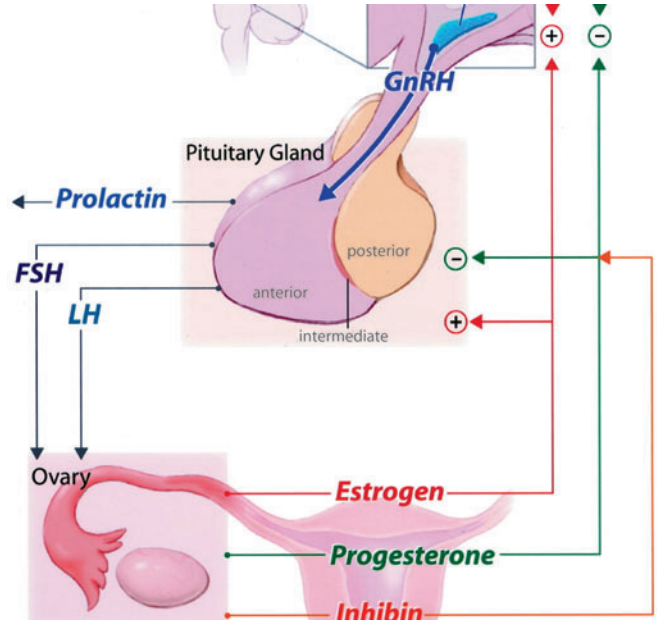

Fig. 3 HPO axis

Fig. 4 Causes of anovulation

Anovulation	
Central Defects	**Peripheral defects**
Adolescence	Premature ovarian failure
Thyroid disease	Ovarian masses
Hyperprolactinemia	Iatrogenic (radiation chemotherapy)
PCOS	Androgen secreting tumors
Hypothalamic dysfunction	Hypogonadism (Turner Syndrome)
Lactation	
Pregnancy	
Perimenopause	
Primary pituitary disease	

in uncontrolled proliferation and unpredictable sloughing (Speroff and Fritz 2004).

The initial presentation of patients with ovulatory dysfunction may be after a prolonged heavy menses or noncyclic bleeding. Upon further questioning, patients usually report episodic periods of amenorrhea depending on the degree of anovulation.

3.2.2 Diagnostics

Diagnosis is aimed toward identifying central defects at the level of the hypothalamus or pituitary versus peripheral defects at the level of the ovaries that ultimately guide treatment (Fig. 4). Age should be considered in evaluation. Anovulation is the most common etiology of abnormal uterine bleeding in adolescence. Please refer to chapter on "► Abnormal Bleeding in Adolescents." Polycystic ovarian syndrome (PCOS) is common in women with anovulatory bleeding 19–39 years of age. Anovulatory bleeding is also common in women 40 years of age until menopause, but endometrial hyperplasia and cancer should be ruled out.

Physical exam findings of hirsutism, obesity, and acanthosis nigricans may suggest syndromes like PCOS. In addition endocrine disorders like thyroid disease and prolactinemia can also lead to hormonal derangements that inhibit ovulation. Laboratory evaluation should include pregnancy testing for sexually active women, thyroid-stimulating hormone, and prolactin. If PCOS is suspected, androgen levels should be drawn to help establish the diagnosis. Please refer to the chapter on "► Evaluation and Management of PCOS."

Imaging is useful in excluding structural causes and evaluation of the adnexa for polycystic ovarian appearance or neoplasms.

Endometrial biopsy can be helpful in determining if ovulation has occurred, with evidence of secretory endometrium and evaluating for endometrial hyperplasia or cancer.

3.2.3 Treatment

The primary goal of treatment, when possible, is to reverse the effects of anovulation as long-term impact of unopposed estrogen has been linked to atypical endometrial hyperplasia and ultimately adenocarcinoma. Central defects that result as a complication of other systemic disorders like hyperthyroidism should be corrected. The alternative approach, for central defects that may not be easily corrected, is to mimic the hormonal changes that naturally occur with ovulation with oral progestins or combined oral contraceptive pills, contraceptive patches, or contraceptive vaginal ring. Progestin-only therapies include the cyclic or continuous oral progestin therapy, levonorgestrel-releasing intrauterine system, or depot medroxyprogesterone acetate (Ammerman and Nelson 2013). There is insufficient evidence to recommend whether progestin alone or in combination with estrogen is more effective in treating AUB-O (Hickey et al. 2012). Patient preference and medical comorbidities and need for contraception should be considered in selecting the best therapeutic option. Treatment recommendations for management of acute uterine bleeding include: DMPA 150 mg IM plus 200 mg oral MPA 20 mg every 8 hours × 9 doses) (Ammerman and Nelson 2013), oral medroxyprogesterone acetate 20 mg 3 times daily × week and then 20 mg daily × 3 week, and a monophasic combination OC containing 1 mg norethindrone and 35 mug of ethinyl estradiol three times per day × 7 days and then one daily for 3 weeks (Munro et al. 2006).

Patients with ovulatory dysfunction who have contraindications to or fail medical therapy or are unable to tolerate side effects or resultant bleeding profile may be considered for surgical management. Surgical options include endometrial ablation, uterine artery embolization, and hysterectomy. If a patient choses ablation or uterine artery embolization, she should be counseled on the risks regarding ability to detect endometrial cancer and that the procedures do not provide contraception.

3.3 Endometrial

Endometrial causes of abnormal uterine bleeding encompass nonstructural pathology involving the lining of the uterus excluding hyperplasia and malignancy. Bleeding is typically described as cyclic and regular but heavy or prolonged in duration. Initial evaluation involves excluding other likely etiologies. When no other etiology of AUB is identified, there is likely a primary disorder of the endometrium. The endometrium is a dynamic structure that undergoes a number of biochemical and morphological changes throughout the menstrual cycle. Aberrations in the biochemical composition may result to impaired vasculogenesis and vasoconstriction. Local synthesis of vasoconstrictors such as endothelin and prostaglandin $F_{2\alpha}$ may be deficient, or plasminogen and vasodilators such as prostaglandin E_2 and prostacyclin I_2 may be increased (Gleeson 1994; Smith et al. 1981).

Current laboratory assessment of disruptions in endometrial stability is limited and the diagnosis is presumptive. Endometrial biopsy may demonstrate acute or chronic endometritis, but the

etiology and clinical significance of chronic endometritis as a cause of AUB is still unclear (Pitsos et al. 2009; Heatley 2004). One study has suggested that over 70 percent of chronic endometritis resulted from mycoplasma infection (Cicinelli et al. 2008). For patients with chronic endometritis treatment with doxycycline 100 mg BID × 14 days is recommended. Subclinical chlamydial infection may also be identified in patients with AUB and should be treated accordingly.

Nonsteroidal anti-inflammatory agents such as ibuprofen 800 mg TID or Naproxen 500 mg BID (Lethaby et al. 2007) or plasminogen inhibitors such as tranexamic acid may be used for patients without a clear infectious etiology.

3.4 Iatrogenic

Medical and surgical interventions may cause AUB. This may be easily elicited by history of any medication use and surgical procedures.

Unscheduled bleeding can occur with cyclic or continuous OCPs, contraceptive patches or rings, medicated and inert intrauterine devices, and injectable or implantable progestins. When the medication is dependent on consistent use, breakthrough bleeding is commonly attributed to erratic compliance. Long-acting reversible contraceptive methods may be more suitable if compliance is an issue. Patients should be counseled that irregular bleeding might still occur in the first several months of use. Endometrial polyp formation in menopausal women on hormone therapy may be dependent on the dosage and type of estrogen and progestogen used (Oguz et al. 2005).

Medications that cause hyperprolactinemia can contribute to AUB. The use of antipsychotics, antidepressants, antihypertensive, and bowel motility agents can result in hyperprolactinemia-induced menstrual disturbances (Molitch 2005). In cases of medication-induced AUB, either medication substitution may help or bleeding may be regulated with similar treatments as mentioned in AUB-O.

Anticoagulation therapy can also cause abnormal uterine bleeding and should be treated similarly to AUB-C. However, antifibrinolytic therapy and estrogen-based therapies are contraindicated.

3.5 Not Yet Specified

When thorough assessment yields no clear etiology, other entities such as arteriovenous malformations and myometrial hypertrophy have been suggested as causes for AUB. The clinical significance of these findings is still unclear. There may be evidence to suggest other causes in the future that will result in modifications to the current classification system. Empiric treatment with any of the suggested options above should be tailored to the woman's contraceptive needs, plans for fertility, pain management, and comorbidities.

4 Conclusion

Given that many causes for AUB exist, a thorough history, physical examinaton, and diagnostic evaluation can easily be completed with an understanding of the most common diagnoses in mind. The current FIGO classification system can be a useful tool in systematically evaluating patients with AUB and facilitating individualized therapy that is evidenced based.

5 Cross-References

- ▶ Conservative Management of Endometrial Cancer: Advantages and Risks
- ▶ Diagnosis and Management of Endometrial Cancer
- ▶ Management of Uterine Fibroids
- ▶ Office and Operative Hysteroscopy
- ▶ Workup and Management of Polycystic Ovary Syndrome

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Laparoscopic Myomectomy: Best Practices

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Contents

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Abstract

Leiomyomas are common pelvic tumors that can cause abnormal uterine bleeding, bulk-related symptoms, and possible effects on fertility and pregnancy. Myomectomy is a surgical treatment option for women who desire uterine preservation. A laparoscopic approach provides the benefits of minimally invasive surgery while achieving similar outcomes to those of open myomectomy. Appropriate patient selection, thorough patient counseling, careful preoperative preparation, and proper surgical technique are paramount to the success and safety of this procedure.

Keywords

Fertility preservation • Fibroid • Laparoscopy • Leiomyoma • Minimally invasive • Myoma • Myomectomy • Uterine preservation

1 Introduction

Leiomyomas, also known as fibroids or myomas, are benign monoclonal smooth muscle tumors. They are the most common type of pelvic tumor in women with a reported incidence of 70–80% by the age of 50 years (Baird et al. 2003). Although many women are asymptomatic, leiomyomas can cause a variety of symptoms, resulting in significant morbidity and high economic burden. Accordingly, many treatment options, both medical and surgical, are available. Women who desire uterine preservation for fertility or other reasons often opt for myomectomy. This procedure can be performed via laparotomy (i.e., abdominal myomectomy) or by use of minimally invasive techniques. Laparoscopic myomectomy is an effective treatment option for appropriately selected patients in whom leiomyoma characteristics preclude a hysteroscopic or vaginal approach.

2 Indications for Myomectomy

The indications for myomectomy are somewhat subjective as they are based on the effects of leiomyomas on the patient's quality of life and daily activities. Many women with leiomyomas are largely asymptomatic; it is difficult to justify any intervention, surgical or otherwise, in these patients. The principal symptoms associated with leiomyomas include abnormal uterine bleeding (with or without anemia), pelvic pressure and pain (caused by uterine bulk and, occasionally, leiomyoma degeneration), urinary and gastrointestinal symptoms (e.g., urinary frequency, incontinence, hydronephrosis, and/or constipation resulting from uterine mass effect on the urinary and gastrointestinal systems), and effects on fertility and pregnancy.

Of these indications, the effects of leiomyomas on fertility and pregnancy may be the most controversial. Indeed, there are no high-quality data that prove that leiomyomas decrease fertility or increase the risk of adverse obstetric outcomes. However, the data that are available do support this notion. Retrospective studies demonstrate that endometrial cavity-distorting leiomyomas (i.e., submucosal leiomyomas or intramural leiomyomas with an intracavitary component; International Federation of Gynecology and Obstetrics [FIGO] types 0, 1, 2, and 3) are associated with decreased fertility outcomes (e.g., clinical pregnancy, implantation, and live birth rates) and that these outcomes are improved with myomectomy. Subserosal leiomyomas (FIGO types 5, 6, and 7) do not affect fertility and therefore should not be removed solely for this indication. Intramural leiomyomas that do not distort the endometrial cavity (FIGO types 3 and 4) are also associated with decreased fertility, but myomectomy has not been shown to improve outcomes (Pritts et al. 2009). The mechanism by which non-cavity distorting intramural leiomyomas affect fertility remains unclear but may be related to the influence of these leiomyomas on endometrial receptivity (Rackow and Taylor 2010).

Available data also demonstrate that leiomyomas are associated with slightly increased risks of adverse obstetric outcomes, including abnormal placentation, fetal malpresentation, preterm premature rupture of membranes (PPROM), placental abruption, preterm delivery, cesarean delivery, intrauterine fetal demise, and postpartum hemorrhage. However, the odds ratios for almost all of these outcomes are less than 2.0, indicating

that the absolute risks, although statistically significant, are relatively low (Qidwai et al. 2006; Stout et al. 2010). Surgical intervention to decrease the risks of future adverse obstetric outcomes should be balanced with the risks of preconception myomectomy.

3 Benefits of Laparoscopy

The advantages of laparoscopy over laparotomy are well established and include decreased morbidity and shorter recovery. Studies show that, compared to open myomectomy, laparoscopic myomectomy is associated with increased operative time but decreased intraoperative blood loss, smaller drop in hemoglobin, decreased postoperative pain, more patients fully recovered by postoperative day number 15, and fewer overall complications. Furthermore, the incidence of major complications (e.g., hemorrhage, visceral injury, thromboembolism), new leiomyoma formation, and pregnancy was not significantly different between laparoscopic and open approaches (Jin et al. 2009). Available data also demonstrate that laparoscopic myomectomy results in less adhesive disease which may affect fertility and subsequent small bowel obstruction (Bulletti et al. 1996).

4 Patient Selection

The wide application of laparoscopic myomectomy is limited by the characteristics of leiomyomas that can be feasibly removed by this approach and the availability of gynecologic surgeons with advanced laparoscopic skills (i.e., laparoscopic suturing). The location, size, and number of leiomyomas determine whether or not a patient is a candidate for laparoscopic myomectomy, although these parameters vary with surgical expertise.

Subserosal leiomyomas (FIGO types 5, 6, and 7), especially those that are pedunculated (FIGO type 7), are the easiest to remove laparoscopically. However, completely intramural leiomyomas (FIGO types 3 and 4) can also be excised with this approach. Some surgeons feel comfortable removing submucosal leiomyomas as well, although these are more often removed with hysteroscopy, depending on their size. If only relatively small FIGO type 0, 1, or 2 leiomyomas are to be removed, then a hysteroscopic approach should be used. Anterior and fundal leiomyomas are often easier to remove than are posterior leiomyomas. Proximity to important structures such as the uterine cornua and the uterine vessels should also be considered. Performing a laparoscopic myomectomy on large and/or many leiomyomas may be time-consuming because morcellation is usually necessary. Removal of such leiomyomas may also result in increased intraoperative blood loss.

The optimal criteria for laparoscopic myomectomy have not been established and depend on the experience and skill of the surgeon. The largest study to investigate this issue included 2,050 laparoscopic myomectomies and concluded that the following leiomyoma characteristics were associated with a significant increase in major complications (e.g., hemorrhage, visceral injury, failure to complete the planned procedure): size greater than 5 cm, total number removed more than three, and intraligamentous location (Sizzi et al. 2007).

Myomectomy should be considered in any patient with symptomatic uterine leiomyomas who desire uterine preservation for the purposes of fertility or other personal reasons. Laparoscopic myomectomy should not be performed in women in whom uterine preservation is contraindicated (e.g., uterine or cervical malignancy) nor in women in whom laparoscopy is contraindicated (e.g., due to medical comorbidities).

5 Preoperative Evaluation and Preparation

5.1 History and Physical Exam

Preoperative evaluation should start with a detailed history of the patient's leiomyoma-related symptoms, such as abnormal uterine bleeding or bulk symptoms. It is important to document how these symptoms affect her quality of life and daily activities. If abnormal uterine bleeding is present, then the patient should also be asked about the presence of symptoms of anemia. The medical history should

include questions regarding a personal or family history of bleeding or clotting disorders, as well as other medical comorbidities which may affect the patient's ability to tolerate general anesthesia and laparoscopic surgery.

A thorough pelvic examination should be performed. On bimanual examination, uterine size, contour, and mobility should be noted along with any other abnormal findings such as the presence of adnexal masses. A fibroid uterus is usually enlarged, irregularly contoured, and/or firm on examination. Examination findings help guide surgical planning and the need for further evaluation including imaging studies.

5.2 Laboratory Tests

As significant blood loss can occur during myomectomy, a blood type and screen as well as a complete blood count should be performed, especially if a history of anemia is present or suspected. Further evaluation for bleeding disorders such as von Willebrand disease should be performed in the presence of other suggestive symptoms or signs, such as a history of heavy menstrual bleeding since menarche.

Premenopausal women aged 45 years or older with abnormal uterine bleeding and postmenopausal women with any uterine bleeding should undergo endometrial sampling to rule out endometrial hyperplasia and malignancy. Endometrial sampling should also be performed in women younger than 45 years with a history of unopposed estrogen exposure (e.g., obesity, polycystic ovarian syndrome), failed medical management, and persistent abnormal uterine bleeding (American College of Obstetricians and Gynecologists 2012). The presence of a uterine malignancy is a contraindication to myomectomy.

5.3 Imaging Studies

Clinically significant subserosal and intramural fibroids can usually be palpated on bimanual examination. Imaging studies can be used to confirm the presence, number, location, and size of leiomyomas. They can also detect the presence of other lesions, such as adnexal masses, that may impact surgical planning. Typically, pelvic ultrasound using a combination of transabdominal and transvaginal approaches is the initial study performed as it is the most readily available and least costly imaging technique. Ultrasonography is reasonably reliable for the evaluation of smaller uteri with four or fewer leiomyomas. Saline infusion sonohysterography, during which saline is injected into the endometrial cavity to provide uterine distension, allows for better delineation of submucosal leiomyomas and their intracavitary involvement. However, ultrasound has significant operator-dependent variability, resulting in inconsistent accuracy and poor reproducibility. Furthermore, ultrasonography has a limited field of view and does not capture most anatomic landmarks, making it difficult to use its images to create a three-dimensional representation of the uterus and its adjacent anatomy (Falcone and Parker 2013).

Pelvic magnetic resonance imaging (MRI) has been shown to have superior sensitivity and reproducibility in the detection of leiomyomas when compared to other imaging modalities, including ultrasonography, saline sonohysterography, and hysteroscopy (Dueholm et al. 2001). More accurate information regarding leiomyoma number, location, and size helps determine if a laparoscopic approach is feasible for myomectomy. Furthermore, tactile sensation is limited during laparoscopy, unlike during open myomectomy in which even small leiomyomas can be palpated. MRI may help a laparoscopic surgeon localize smaller leiomyomas intraoperatively.

MRI is considered the best imaging modality for the detection of adenomyosis, a condition characterized by the presence of endometrial glands within the myometrium (Champaneria et al. 2010). Adenomyosis can mimic leiomyomas in its clinical presentation as both can cause abnormal uterine bleeding, abdominal/pelvic pain, and uterine enlargement. MRI features consistent with adenomyosis include poor definition and thickening of the junctional zone (the interface between the endometrium and the myometrium) greater than 12 mm (Gordts et al. 2008).

Pelvic MRI is also indicated if uterine sarcoma is suspected. Due to their increased vascularity, leiomyosarcomas may demonstrate increased enhancement on gadolinium-enhanced timed MRI. Elevated serum total lactate dehydrogenase (LDH) and LDH isoenzyme-3 should also raise concern for leiomyosarcoma (Goto et al. 2002). Although rapid growth of a uterine mass (i.e., increasing by 6 weeks' gestational size within 1 year) being a sign of a potential uterine sarcoma is a commonly held belief, it has been shown that this is almost never true in premenopausal women (Parker et al. 1994). Ultimately, women in whom there exists a strong preoperative suspicion for uterine sarcoma or other uterine malignancy should not undergo laparoscopic myomectomy.

5.4 Informed Consent

Preoperative informed consent should include a discussion of alternatives to myomectomy, including expectant management, medical management, interventional radiology procedures such as uterine leiomyoma embolization and magnetic resonance-guided focused ultrasound, and other surgical options. Hysterectomy should be discussed with women who are not interested in preserving fertility as quality-of-life outcomes may be better than those with myomectomy (Spies et al. 2010).

Possible complications of myomectomy should be discussed. Complications include excessive bleeding requiring blood transfusion or, in the rare situation that life-threatening bleeding occurs and is unable to be controlled with other measures, hysterectomy. Patients who plan to become pregnant should be counseled about the potential need for cesarean delivery and the risk of uterine rupture. New leiomyoma formation and recurrence or persistence of leiomyoma-associated symptoms should also be discussed. Conversion to laparotomy is a possibility with all laparoscopic procedures.

Leiomyoma morcellation, if planned, must be discussed in detail. The safety of power morcellation during laparoscopic myomectomy and hysterectomy has recently come into question by the United States Food and Drug Administration (FDA), prompted by a widely publicized case report in which morcellation was used in the presence of an undiagnosed leiomyosarcoma. After performing a limited literature review which included nine studies, the FDA concluded that 1 in 350 women undergoing hysterectomy or myomectomy for the treatment of leiomyomas is found to have an unsuspected uterine sarcoma (U.S. Food and Drug Administration 2014). Subsequent literature reviews and case series have yielded a much lower incidence, as low as 1 in 1,960 women per a meta-analysis of 133 studies (Pritts et al. 2015). Patients should be counseled about the prevalence of uterine sarcoma and the possible risks of morcellation in the setting of an undiagnosed malignancy. Other risks of morcellation, including visceral injury, should also be discussed.

The informed consent discussion should be documented in the medical record and on the surgical consent form.

5.5 Managing Preoperative Anemia

Anemia resulting from heavy menstrual bleeding is a common symptom of leiomyomas. Preoperative anemia increases the risks of blood transfusion and perioperative morbidity and mortality. Iron supplementation is often used to increase preoperative hemoglobin levels. Oral iron is first-line therapy in nonurgent situations due to its ease of administration and cost-effectiveness. However, the response is relatively slow, requiring at least 1–2 weeks before any increase in hemoglobin occurs, and patients often report gastrointestinal side effects. Intravenous iron produces a more rapid rise in hemoglobin without gastrointestinal side effects but has the potential to cause allergic reactions including anaphylaxis, although rare. Epoetin, a recombinant form of erythropoietin, a hormone that stimulates red blood cell production, can also produce more rapid correction of preoperative anemia but is more expensive than iron supplementation.

Another approach toward the management of preoperative anemia is to treat the patient's heavy

menstrual bleeding while she is awaiting surgery, resulting in an increase in hemoglobin. Pharmacologic agents that can induce amenorrhea include gonadotropin-releasing hormone (GnRH) agonists, continuous combined oral contraceptive pills, and oral progesterone. Many surgeons report that, in patients with prior GnRH agonist use, leiomyoma enucleation is noticeably more difficult because the tissue plane between the leiomyoma and the myometrium becomes obscured; however, this belief has not been proven in any study.

6 Operative Technique

6.1 Anesthesia and Patient Positioning

As with most laparoscopic gynecologic procedures, the patient should be placed under general endotracheal anesthesia and in the supine or lithotomy position. Lithotomy is required if the surgeon chooses to place a uterine manipulator which can be used to improve intraoperative visualization. A uterine manipulator also allows for instillation of indigo carmine or methylene blue dye if chromopertubation is planned or to determine if the endometrial cavity is entered during the procedure. The patient should also be placed in lithotomy if concomitant hysteroscopy is performed. Tucking of the bilateral upper extremities often provides surgeons with the best access to the operative field. Adequate intravenous access should be established by the anesthesiologist before the arms are padded and tucked. Both the abdomen and the vagina are surgically prepared. An indwelling catheter is inserted into the bladder to decrease the risk of intraoperative bladder injury and to monitor urine output. The catheter can also be used to backfill the bladder should delineation of its borders become necessary.

6.2 Prophylaxis

Virtually all laparoscopic myomectomies are at least 30 minutes in duration and are therefore considered major surgeries. As such, they pose at least low to moderate risk of venous thromboembolism. Therefore, prior to induction of anesthesia, each patient should receive venous thromboembolism prophylaxis, mechanical and/or pharmacologic, tailored to her individual risk factors, or lack thereof (American College of Obstetricians and Gynecologists 2007). A benefit of laparoscopic surgery is that patients regain postoperative mobility more rapidly than after laparotomy, thereby decreasing the risk of postoperative venous thromboembolism.

Antibiotic prophylaxis is not indicated for laparoscopic procedures. The risk of surgical site infection is low in procedures during which the bowel or vagina is not entered (American College of Obstetricians and Gynecologists 2009).

6.3 Laparoscopic Port Placement

Laparoscopic port placement is based on the location and size of the leiomyomas to be removed. The initial port is often placed at the umbilicus but may also be placed in the left upper quadrant (i.e., Palmer's point) if the uterine fundus is at or above the umbilicus or if significant umbilical adhesions are anticipated. Once the initial port is placed, the laparoscope is inserted into the peritoneal cavity and the abdomen and pelvis are examined. If there are findings that preclude safe completion of a laparoscopic myomectomy such as the presence of extensive adhesive disease, then the procedure should be converted to laparotomy.

Typically, three additional laparoscopic ports are placed. To make laparoscopic suturing more ergonomic, two right-sided ports are placed if the surgeon is right-handed or two left-sided ports if the surgeon is left-handed. The first port is placed approximately 2 cm superior and medial to the anterior superior iliac spine. This port can be 12 mm in size to allow for the passage of curved needles for suturing and for the insertion of the morcellation device, if used. A second, 5 mm port is placed medial and slightly superior to the first port. Another 5 mm port is placed in the contralateral lower quadrant.

6.4 Strategies to Decrease Intraoperative Blood Loss

Intraoperative blood loss can be decreased with pharmacologic and/or mechanical intervention. Perhaps the method most commonly used during laparoscopic myomectomy is the use of vasopressin, a pharmacologic agent that causes vasoconstriction. Vasopressin is injected into the myometrium at the site of the planned uterine incision. Injection can be performed using a long needle inserted through a laparoscopic port or directly through the anterior abdominal wall. Care should be taken to avoid intravascular injection by withdrawing the plunger of the syringe to check for blood prior to injection. Even in the absence of intravascular injection, vasopressin can cause systemic hemodynamic changes and has been associated with rare cases of cardiovascular collapse and death (Falcone and Parker 2013). Clear communication should occur between the surgeon and the anesthesiologist; the surgeon should notify the anesthesiologist when vasopressin is being administered, and, in turn, the anesthesiologist should notify the surgeon of any signs of hemodynamic instability in the patient. Furthermore, a maximum dose of vasopressin should be determined prior to surgery. Although the maximum safe dose of vasopressin has not been definitively established, a total dose of 4–6 units per procedure is widely used. Dilution of the vasopressin (e.g., 20 units of vasopressin in 100 ml of normal saline) helps to limit the total dose (Frishman 2009).

Uterotonics have also been used to decrease intraoperative blood loss. Small studies have demonstrated that both vaginal dinoprostone and vaginal misoprostol significantly decrease blood loss during myomectomy; however, the latter has not been shown to decrease the risk of blood transfusion. There is no evidence that the use of oxytocin decreases intraoperative blood loss or the risk of blood transfusion (Kongnyuy and Wiysonge 2014).

Mechanical interventions, such as the use of tourniquets or clamps, can be used to decrease intraoperative blood loss by occluding the uterine blood supply from the uterine and ovarian arteries. However, it is difficult to secure a tourniquet using laparoscopic instruments. Accordingly, they are not used as often during laparoscopic myomectomy as they are during open myomectomy.

Intraoperative blood salvage (e.g., Cell Saver) may be used in procedures in which significant blood loss is anticipated, thereby avoiding allogeneic blood transfusion and its associated complications. This technology involves suction of blood from the surgical field, separation and washing of the red blood cells, and eventual reinfusion to the patient. Intraoperative blood savage is less commonly used during laparoscopic myomectomy than during open myomectomy, likely because significant blood loss is more often anticipated during the removal of leiomyomas with characteristics that require an open approach.

6.5 Uterine Incision and Leiomyoma Removal

A transverse incision is made on the uterus directly over the leiomyoma and extended deeply until the leiomyoma is clearly seen. A monopolar device such as the hook or an ultrasonic cutting and coagulating device such as the Harmonic scalpel may be used. The transverse direction allows for more ergonomic suturing of the uterine defect when compared with a vertical incision. Care should be taken to avoid the uterine cornua, the ascending uterine artery and venous plexus lateral to the uterus, and the site where the uterine artery enters the uterus at the level of the internal cervical os. The leiomyoma is grasped with a tenaculum to provide traction. A combination of traction and countertraction, blunt and sharp dissection, and/or electrosurgery is used to dissect under the pseudocapsule and separate the plane between the leiomyoma and the surrounding myometrium, thereby enucleating the leiomyoma.

6.6 Repair of Uterine Defects

As is performed during an open myomectomy, all uterine incisions are closed in one or more layers, depending on the depth of the incision. Size

0 delayed absorbable suture such as poliglecaprone (Monocryl) or polydioxanone (PDS) is often used. Polyglactin (Vicryl) is another option but has a higher friction coefficient which may cause more fraying of the suture with extracorporeal knot tying. Absorbable barbed suture may also be used to close the myometrium. This suture not only obviates the need for knot tying but also maintains tension on the myometrium, thereby facilitating laparoscopic suturing. Indeed, expeditious closure of uterine defects significantly reduces intraoperative blood loss.

6.7 Morcellation of Leiomyomas

For leiomyomas that are too large to be removed from the abdomen directly through one of the laparoscopic port sites, morcellation can be accomplished by using an electromechanical device or manually by using a scalpel. Both techniques can be performed in an uncontained fashion or in a contained fashion within an extraction bag. To decrease the risk of visceral injury, the blade of the morcellation device should be under direct laparoscopic visualization at all times, including during its insertion and removal from the abdomen. The blade should also be directed toward the anterior abdominal wall as much as possible. After all leiomyomas have been morcellated, the device should be removed from the abdomen and a thorough inspection of the peritoneal cavity for tissue fragments must be performed. Copious irrigation and suctioning should be used to remove blood and any smaller tissue fragments.

6.8 Closure

At the close of the procedure, hemostasis should be assured throughout the peritoneal cavity. Measures to prevent adhesion formation, such as placement of adhesion barrier products (e.g., Interceed, Seprafilm), may be taken if desired. The fascia of any laparoscopic port site that is 10 mm or larger should be closed to decrease the risk of incisional hernia development (Boike et al. 1995).

7 Complications

Complications of laparoscopic myomectomy are similar to those of open myomectomy, including blood loss, infection, and adhesion formation. Complications unique to a laparoscopic approach include conversion to laparotomy and those related to trocar insertion, such as trocar-related bowel or vascular injury.

8 Postoperative Care

Laparoscopic myomectomy is typically performed as an outpatient procedure. Overnight inpatient observation may also be considered. The patient may resume her routine activities including vaginal intercourse as soon as she feels comfortable. She may return to work once she has regained sufficient strength and mobility, usually within 2 weeks. A routine postoperative outpatient visit should occur within 2–6 weeks. During this visit, details of the surgery and pathology results are reviewed, the abdomen and incisions are examined, the uterus is evaluated for hematoma formation, and the patient is evaluated for any potential complications.

9 Outcomes

9.1 Improvement of Symptoms

Although there is currently no data regarding the rate of symptom relief following laparoscopic myomectomy, success rates may be extrapolated from data for open myomectomy, which has been reported to provide symptom relief in approximately 80% of patients (Broder et al. 2002).

9.2 New Leiomyoma Formation

The rate of new leiomyoma formation at 5 and 8 years after myomectomy has been reported to be 53% and 85%, respectively. However, rates of reoperation, arguably more significant for

patients, were much lower at 7% and 16%, respectively. Risk factors for new leiomyoma formation include multiple leiomyomas present at the time of surgery, uterine size of 13 weeks or larger, and age younger than 36 years (Yoo et al. 2007). The rate of new leiomyoma formation is not significantly different between laparoscopic myomectomy and open myomectomy (Jin et al. 2009).

10 Pregnancy After Myomectomy

10.1 Interval to Conception

It is recommended that patients wait at least 3 months after myomectomy before attempting to conceive. A small prospective study used serial MRI to investigate the amount of time necessary for the uterine structure to reach a stable state following myomectomy. The authors concluded that the recovery process is complete at 12 weeks in the absence of hematoma or edema formation in the myometrium on MR images (Tsuji et al. 2006).

10.2 Risk of Uterine Rupture

Although cases of uterine rupture during labor in patients with prior myomectomy have been reported, the actual risk of rupture and the factors associated with an increased risk are unknown. Myomectomy in which the endometrial cavity is entered or the myometrium is otherwise significantly compromised is thought to incur risk similar to that of a prior classical cesarean delivery, the reported incidence of which ranges from 1% to 12%. Accordingly, it is recommended that women with prior myomectomy in which the myometrium may have been significantly compromised be delivered by cesarean delivery at 36–38 weeks of gestation. Myomectomy in which only pedunculated leiomyomas (FIGO type 7) are removed is thought to incur significantly less risk of uterine rupture. Therefore, women with prior myomectomy requiring minimal or no myometrial dissection are given the option of a trial of labor (Spong et al. 2011).

It has been argued that the risk of uterine rupture following laparoscopic myomectomy is higher than that following open myomectomy, possibly due to the technical challenge of laparoscopic suturing. However, more recent studies have demonstrated that the incidence of uterine rupture following myomectomy is similar between laparoscopic and open approaches (Flyckt and Falcone 2015). Multiple-layer closure of uterine defects and prudent use of electrosurgery are recommended to limit this risk (Parker et al. 2010).

11 Conclusion

Laparoscopic myomectomy is a safe, effective, and minimally invasive alternative to open myomectomy for women with symptomatic uterine leiomyomas who desire uterine preservation. Thorough preoperative evaluation and preparation ensure that appropriate patients are selected for this surgery. Outcomes are similar to that of open myomectomy while providing the benefits of decreased morbidity and quicker recovery that are afforded by laparoscopy. The wide application of laparoscopic myomectomy is limited by certain leiomyoma characteristics and the availability of gynecologic surgeons with advanced laparoscopic skills.

12 Cross-References

- ▶ Laparoscopic Hysterectomy
- ▶ Management of Abnormal Bleeding in Late Reproductive Years
- ▶ Management of Uterine Fibroids

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Laparoscopic Hysterectomy

Alexander Chiang, Steve Yu, and William Parker

Abstract

Laparoscopic hysterectomy is a minimally invasive surgical technique for removal of the uterus. It is more commonly performed than the vaginal hysterectomy. The laparoscopic approach has better outcomes compared with an abdominal hysterectomy. Laparoscopic hysterectomy can be used for treatment of abnormal uterine bleeding, uterine fibroids, pelvic pain, and premalignant and malignant gynecologic conditions involving the uterus. Alternatives to hysterectomy should always be discussed when possible and appropriate. The appropriate selection for a laparoscopic hysterectomy is largely based on the surgeon's experience and skill and the preference of the patient.

Keywords

Laparoscopic hysterectomy • Laparoscopy • Minimally invasive gynecologic surgery • Uterine fibroid • Uterine leiomyoma • Endometriosis

Contents

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1 Introduction

Laparoscopy is a diagnostic and therapeutic surgical procedure that uses a laparoscope attached to a video camera. The procedure is considered minimally invasive because the incisions on the abdomen are significantly smaller than the traditional open surgery. For instance, most laparoscopic instruments will fit through an opening of 5 mm. The abdomen is insufflated with carbon dioxide (CO_2) gas, which is bio-inert and nonflammable. Access into the abdomen is provided by laparoscopic ports, also known as trocars, that allow easy insertion and exchange of the camera and/or surgical instruments. The trocars also function as a valve, preventing the loss of gas during surgery. In other words, it maintains pneumoperitoneum allowing adequate visualization during the case. The first trocar inserted into the abdomen is referred to as the primary trocar. All subsequent trocars are called secondary.

Laparoscopic surgical procedures have been developed for most surgical procedures that were previously only done by laparotomy. In gynecology, laparoscopy is performed for most surgeries including, but not limited to, hysterectomy, cystectomy, oophorectomy, sterilization, salpingectomy, myomectomy, and cancer staging procedures.

Hysterectomy used to be the second most common surgical procedure after cesarean section in the 1980s to early 2000s. Currently, the numbers have declined from approximately 600,000 per year to 480,000 per year as of the latest census in 2009. Hysterectomy is now the seventh most common surgical procedure performed in the United States (Fingar et al. 2014). Many alternatives to hysterectomy, both medical and surgical, have contributed to this decline. The first laparoscopic hysterectomy was performed in 1989 (Reich et al. 1989). Since then, as surgeons have become better trained in laparoscopic surgery, there has been an increasing trend toward the use of laparoscopic hysterectomy. According to the 2009 census, approximately 20% of all hysterectomies for benign disease were performed by laparoscopy. Abdominal hysterectomy comprises approximately 56%, vaginal hysterectomy 19%, and robotic 5% of all hysterectomies (Cohen et al. 2014).

2 Types of Hysterectomy

Hysterectomies can be divided into total (removal of the cervix with the uterus) or supracervical (removal of the uterine corpus without the cervix). A supracervical hysterectomy is also called a partial or subtotal hysterectomy. In gynecologic oncology cases, radical hysterectomies (a total hysterectomy including the parametria) can also be performed to obtain wider margins.

Routes of hysterectomy include:

- Vaginal hysterectomy
- Laparoscopic or robotic-assisted laparoscopic hysterectomy
- Abdominal (open) hysterectomy

Laparoscopic hysterectomies can be subdivided into:

- Total laparoscopic hysterectomy: the uterus and cervix are removed en bloc through the vagina or morcellated (cut and removed in smaller pieces) and removed through the trocars. After removal of the cervix, the resulting vaginal cuff (the proximal opening of the vagina where the uterus was amputated) is sutured closed.
- Laparoscopic supracervical hysterectomy: the uterus is at the level of the cervix, which is left intact. The uterus must be morcellated in order to extract it or delivered through a minilaparotomy.

- Laparoscopic-assisted vaginal hysterectomy: the round and broad ligaments and possibly the adnexa (ovaries and fallopian tubes) are transected laparoscopically, and the remainder of the hysterectomy is completed vaginally as with a vaginal hysterectomy.
- Robotic-assisted laparoscopic hysterectomy: the laparoscopic camera and instruments are manipulated with a surgeon-controlled computerized robot.

3 Indications

Hysterectomies are commonly performed for abnormal uterine bleeding, pelvic pain, uterine prolapse, and premalignant or malignant conditions. According to a census in 2005, 26.9% of hysterectomies were performed with fibroids as the indication, 25.2% for abnormal uterine bleeding, 16.2% for endometriosis, and 11.7% for pelvic pain (Merrill 2008).

4 Benefits and Risks

Many of the studies assessing the benefit and risk profiles between abdominal, vaginal, and laparoscopic hysterectomies are limited by poor reporting or imprecise data. Any discussion of benefits and risks are ultimately based on the patient's wishes and surgeon's experience and skill set. The risks are generally reduced with increased experience with laparoscopic hysterectomy (usually more than 30 cases (Mäkinen et al. 2013)). In general, there are many benefits to laparoscopic hysterectomy compared to abdominal hysterectomy. The benefits include: reduction in overall morbidity, blood loss, infection, postoperative pain, length of stay in the hospital, and recovery time. Ureteral and bowel injury rates are generally equal between laparoscopic and open procedures (Mäkinen et al. 2013).

Specifically, benefits include:

- Shorter length of stay in the hospital: decreased by 1–3 days for the laparoscopic approach compared to the abdominal approach (Aarts et al. 2015)
- Shorter recovery time: return to normal activities was 36.3 days for the abdominal approach vs 22.7 days for the laparoscopic approach (Aarts et al. 2015)
- Decreased wound infection rates: 2.4% with abdominal and 1.5% with laparoscopic (Mäkinen et al. 2013)
- Fewer thromboembolic events: 0.1% with abdominal vs 0% with laparoscopic (Mäkinen et al. 2013)
- Less significant bleeding (as measured by postoperative hemoglobin drop or need for blood transfusion): 1.6% with abdominal and 0.6% with laparoscopic (Aarts et al. 2015)

The risks of laparoscopic hysterectomy versus abdominal hysterectomy include a higher risk of:

- Vaginal cuff dehiscence (0.75% in laparoscopic hysterectomies versus 0.38% in abdominal hysterectomies (Hur et al. 2011))
- Bladder injuries (1.0% for laparoscopic hysterectomies versus 0.7% for abdominal hysterectomies (Härkki-Sirén et al. 1998; Mäkinen et al. 2013)
- Vascular injuries (1.6% for laparoscopic hysterectomies versus 0.9% for abdominal hysterectomies (Aarts et al. 2015)
- Increased operating time: 30 min more for laparoscopic hysterectomy (Aarts et al. 2015)

When comparing laparoscopic hysterectomy with vaginal hysterectomy, there is no overall statistically significant difference except a longer operating time for laparoscopic hysterectomy of about 17 min (Aarts et al. 2015).

Increased risks with a laparoscopic hysterectomy have been associated with larger uterine size (or mass) >250–300 g, increased body mass index (or degree of obesity), pelvic adhesive disease such as endometriosis or prior abdominal surgeries, and other comorbidities (e.g., cardiopulmonary disease), or increased concern for malignancy. Consideration and management

strategies for these conditions will be further discussed later in this chapter.

5 Alternatives

Since the late 1990s, viable alternatives to hysterectomy have been further developed due to improvements in medical and surgical therapies.

It is noteworthy that many women with uterine leiomyoma do not need any treatment. Expectant management of fibroids causing nonlife-threatening bleeding or pelvic pressure has been underappreciated. There is some evidence that expectant management is a viable alternative based on several factors including the impact of symptoms such as bleeding or pain on a woman's quality of life and patient age (Reiter et al. 1992). Some women may find their symptoms improve or resolve with menopause.

For patients with pelvic organ prolapse, pelvic floor therapy and pessary usage may provide improvement in symptoms and allow patients to avoid surgery.

5.1 Medical Therapy

Nonhormonal medical treatments are available for abnormal uterine bleeding, symptomatic fibroids, adenomyosis, and endometriosis. A common medication regimen includes high-dose nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or naproxen taken orally to minimize bleeding and pain. NSAIDs can decrease heavy menstrual bleeding from adenomyosis, fibroids, and ovulatory dysfunction and decrease pelvic pain from endometriosis, adenomyosis, and fibroids. Two proteins that mediate coagulation in the endometrium are prostacyclins and thromboxane A2, and their relative levels allow a homeostatic effect for control of bleeding. Prostacyclins inhibit vasoconstriction and the platelet aggregation effect of thromboxane A2. NSAIDs indirectly inhibit prostacyclin synthesis and thus increase the relative effect of thromboxane A2 causing vasoconstriction and platelet aggregation at the site of the uterine endometrial and myometrial vasculature. This leads to attenuation of heavy menstrual bleeding. Additionally with fibroids, endometriosis, and adenomyosis, the anti-inflammatory effects of NSAIDs also block the cytokine cascade of inflammation that causes pain.

Another effective nonhormonal treatment for heavy menstrual bleeding is tranexamic acid (Lysteda), an antifibrinolytic agent that can reduce heavy menstrual bleeding by 26–54% (Milsom et al. 1991). In comparative studies, this medication was more effective than NSAIDs, but not as effective as a levonorgestrel intrauterine system (LNG-IUS) (Milsom et al. 1991). This drug has been used in Sweden since the 1960s for heavy menstrual bleeding and is widely available and affordable in Canada and Europe. It has been available in the United States since the FDA approval in 2009. It has not gained wide popularity due to its high cost. The safety of this medication has been widely studied, and it does not seem to increase the risk of thrombosis; however it is not recommended to use tranexamic acid in conjunction with birth control pills. Tranexamic acid is a safe alternative to hormonal medical management in patients who have contraindications to hormones, such as breast cancer, but also desire to avoid surgery.

Gonadotropin-releasing hormone (GnRH) agonists such as Lupron Depot can be used in cases of symptomatic fibroids, adenomyosis, endometriosis, and ovulatory dysfunction by suppressing ovarian function and decreasing hormonal stimulation of these conditions. This treatment is limited due to the side effects of pharmacologically induced menopause, including hot flashes, vaginal dryness, and headaches and is thus only a temporary solution, usually when the patient is transitioning to menopause or preparing for surgery.

Another hormonal treatment option for both dysmenorrhea and heavy menstrual bleeding is progesterone-only medication such as norethindrone or medroxyprogesterone. These synthetic progestins can cause an attenuation of growth of the endometrial lining and minimize fibroid-

related heavy menstrual bleeding. A similar effect can be seen with the LNG-IUS, also known as the Mirena intrauterine device (IUD) in the United States. This device is placed inside the uterine cavity, and the slowly released levonorgestrel decidualizes the endometrium with subsequent decreased heavy menstrual bleeding or dysmenorrhea. The advantage of the LNG-IUS is that it has a long-acting effect up to 5 years and has minimal systemic progesterone-related side effects such as nausea, bloating, breast tenderness, appetite stimulation, or bone mineral density loss. For younger women not currently desiring fertility, this would have the added benefit of a highly effective, reversible, long-acting contraception. Fibroids distorting the uterine cavity are a contraindication stipulated by the manufacturer if used for contraception due to the increased expulsion rates of 0–20% from a recent systematic review (Zapata et al. 2010). However, if the patient is highly motivated to avoid surgery, this could still be a viable option as long as the patient is counseled on all risks. Furthermore, the patient should also be informed that any progesterone-only method has the risk of causing breakthrough spotting or bleeding, which may also be equally undesired compared with heavy menstrual bleeding. A comparative 10-year study done in Finland in the 2000s showed that for women with heavy menstrual bleeding, 46% of those initially randomized to an IUD ultimately underwent a hysterectomy due to continued symptoms. Satisfaction measured by standardized questionnaires was similarly improved in both the IUD and hysterectomy groups over the first 5 years but returned to baseline for both groups between 5 and 10 years (Heliövaara-Peippo et al. 2013).

5.2 Surgical Therapy

Endometrial ablation is a minimally invasive procedure for the treatment of abnormal uterine bleeding. The general principle involves the use of a heating element to ablate the endometrium, which produces menstrual blood. There are many different devices that have been developed. The procedure usually takes less than 10 min to perform. Endometrial ablation is a popular choice for many patients since it does not require any incisions and the recovery is almost instantaneous. The general contraindications for this procedure include suspected malignancy or malignancy, desire for future childbearing, and a large uterus.

Uterine artery embolization (UAE) is performed by an interventional radiologist. The idea is to occlude the blood supply to the fibroid, causing ischemic degeneration. Over time, the fibroid or fibroids reduce(s) in size, resulting in reduction of uterine bleeding and pain. Uterine artery embolization has been shown to be effective in short- and long-term follow-up studies with 95% of women who underwent this procedure noting a significant improvement of fibroid-related symptoms and quality of life after 3 years. However, 29% of women developed post-procedure amenorrhea, and 14.4% underwent an additional invasive procedure such as hysterectomy (9.8%), myomectomy (2.8%), and a repeat UAE (Goodwin et al. 2008). After 5 or more years, 75% of women who underwent UAE reported normal or improved bleeding, while 20% had undergone an additional invasive procedure (Walker and Barton-Smith 2006). Contraindications include size and types of fibroids (e.g., pedunculated or intracavitary fibroids) and desire for future childbearing. The safety of this procedure with regard to subsequent future fertility and pregnancy is limited by small case series and conflicting results. Slightly increased rates of miscarriage, malpresentation, preterm delivery, and postpartum hemorrhage have been reported (Homer and Saridogan 2010).

Myomectomy is also an alternative to hysterectomy for symptomatic fibroids and can be performed hysteroscopically, laparoscopically, or abdominally depending on the location and size of the fibroid(s). Traditionally, this is performed in women of reproductive age desiring to preserve fertility; however, the rates of myomectomy have increased since the 1990s in women no longer desiring future fertility. In addition to the preservation of the uterus, myomectomy has an additional benefit compared to hysterectomy. The

main blood supply to the ovary is the ovarian artery, which is a direct branch from the aorta. However, some of the ovarian blood supply arises from the uterus. Therefore, after a hysterectomy, about 10% of women undergo menopause 2–3 years before their expected natural time. This iatrogenic effect is not observed after a myomectomy (Farquhar et al. 2005).

6 Surgical Planning

6.1 Preoperative Workup

A thorough medical, surgical, gynecologic, and obstetric history should first be obtained. Any comorbidities that may impact the ability to tolerate surgery should be evaluated and properly assessed. A careful physical examination should be performed with attention to uterine size and shape when considering feasibility of a laparoscopic approach and need for morcellation. Furthermore, the location of potential fibroids specifically in the cervix or posterior lower uterus should be identified as this may make the uterus more difficult to remove. Prior surgical scars and the absence of uterine mobility should be assessed as indicative of possible adhesive disease. Obesity can also alter the ability to successfully complete a surgical procedure, and thus any excessive abdominal pannus should be noted.

Imaging can be very helpful in the majority of hysterectomies. A pelvic ultrasound is generally useful for evaluation of a fibroid uterus and any concomitant adnexal pathology that may also need to be addressed at the time of surgery. Magnetic resonance imaging (MRI) may sometimes help with diagnosis of atypical fibroids or help determine if morcellation should be attempted if leiomyosarcoma is suspected based on imaging. Imaging is not helpful in determining the severity or extent of endometriosis or adhesive disease.

Tissue evaluation with an endometrial biopsy may be necessary for patients at risk for uterine malignancy. Preoperative knowledge of malignancy would change the planning of the surgery by involving a gynecologic oncologist who would perform staging procedures, such as lymph node sampling. A recent pap smear to ensure there is no concomitant cervical cancer is also recommended according to the current American College of Obstetrics and Gynecology (ACOG) guidelines.

The minimum laboratory evaluation should include a complete blood count in cases of acute or chronic abnormal uterine bleeding. A basic metabolic panel should be considered if an obstructive uropathy is suspected from a large pelvic mass. Any additional labs may be necessary depending on other comorbid conditions.

7 Patient-Specific Risk Factors

7.1 Obesity

Laparoscopy can be safely performed on obese patients. The increased degree of difficulty in obese patients can be decreased with robotic-assisted laparoscopy, but this may not improve operating time or costs. Attention to patient positioning with extra cushioning along the joints and extremities is advised. The degree of tilt in the Trendelenburg position may be limited due to increased weight and pressure of the abdominal pannus on the chest compromising the ability to adequately ventilate. This is compounded by the fact that pneumoperitoneum pressures may need to be increased in obese patients in order to improve intra-abdominal visualization. Anti-slip padding and straps should be used to prevent sliding of the patient in the Trendelenburg position. Entry into the abdominal cavity for insufflation via a Veress needle or a direct optical entry technique is still considered easiest at the umbilicus where the distance from the skin into the abdominal cavity is the shortest. An open Hasson entry technique may not be feasible without a larger incision due to the depth of the subcutaneous fat. Central obesity also increases the distance to the aorta, and thus a 90° entry angle will increase successful entry into the abdomen. Longer trocars may be needed depending on the degree of obesity.

7.2 Uterine Size and Contour

The size of the uterus not only plays an important role in determining the route of hysterectomy, but with laparoscopic hysterectomy, large uteri over 16 weeks in size may make visualization of the anterior lower uterine segment and parametria difficult. Limited visualization can prohibit adequate access to the uterine vessels for ligation. An appropriate uterine manipulator and usage of a single tooth tenaculum in the assistant's laparoscopic port may facilitate further caudal and contralateral manipulation of the uterus off the pelvic side wall to improve visualization of the adnexa and uterine vessels. Any fibroids that distort the uterine anatomy such as cervical, broad ligament, or posterior fibroids may preclude completion of a hysterectomy due to limited visualization and access to the uterine vessels or bladder flap. Laparoscopic myomectomy, if feasible, may be necessary prior to completion of the hysterectomy.

7.3 Abdominal and/or Pelvic Adhesive Disease

Prior abdominal surgeries, such as cesarean sections and/or myomectomies, and endometriosis or a history of a prior abdominal infection, such as ruptured appendicitis, may increase the degree of adhesive disease and thus increase the risks of injury to adjacent bowel, bladder, or adnexal organs. Usually, a safe route of entry is at Palmer's point, located approximately 3 cm inferior to the left costal margin along the midclavicular line. If this site of entry is desired, placement of an oral-gastric or nasogastric tube is highly advised in order to decompress the stomach and move the associated small gastric vessels away from the site of entry.

7.4 Concern for Malignancy

If there is a high index of suspicion for a gynecologic malignancy and if the uterus is too large to be extracted through the vagina, then laparoscopic hysterectomy should be avoided. In other words, tissue extraction by morcellation should not be performed if malignancy is suspected. There should be a high level of suspicion if a fibroid increases in size in a postmenopausal woman.

8 Preoperative Preparation

8.1 Prior to the Day of Surgery

A preoperative medical clearance may be needed for significant comorbid conditions. The patient should have an adequate NPO status, usually 8 hours prior to the surgery. In cases of anemia due to abnormal uterine bleeding, an adequate hematocrit level should be achieved with iron supplementation or a blood transfusion perioperatively in cases of acute hemorrhage. Bowel preparation is not necessary, although this is controversial as some surgeons find it beneficial for visualization.

8.2 On the Day of Surgery

The patient is placed under general anesthesia to manage ventilation, while the abdomen is insufflated and the patient is in the Trendelenburg position. Adequate mechanical, pharmacologic, or a combination of both types of thromboprophylaxis should be given. Obese patients have a higher risk of thromboembolism. Antibiotics should be given prior to the start of the case. Typical regimens include a third-generation cephalosporin, such as cefazolin or cefoxitin, or in case of penicillin allergy, clindamycin and gentamicin or metronidazole with either gentamicin or a fluoroquinolone.

The patient should be positioned in a low lithotomy position on the table with antiskid or anti-slippage pads and careful cushioning to avoid neurologic injury but still allow for surgeon position and access to the vagina. The sacrum should be near the end of the operating table. Tucking the arms to the sides of the patient allows more mobility for the surgeon. The anesthesiologist should be notified to ensure adequate access to IV lines and the blood pressure cuff. In patients with a high risk

of blood loss or a low starting hematocrit level, a second large bore IV access should be considered. The chest above the level of the nipples is often strapped or taped to the bed in order to minimize cephalad slippage of the patient while in the Trendelenburg position. Caution must be taken to ensure that the chest strap or taping allows adequate ability to ventilate while under general anesthesia.

A uterine manipulator should be placed for manipulation of the uterus during surgery. This facilitates visualization during surgery, displaces the ureter laterally when ligating and transecting the uterine artery, and delineates the cervicovaginal junction when amputating the uterus and cervix away from the vagina. A bladder catheter should be placed to decompress the bladder.

9 Procedure

Most hysterectomies can be performed with three trocars (the primary and one secondary trocar on each side of the abdomen). Attention should first be focused on what is commonly referred to as the triple pedicles of the uterus. These structures include the round ligament, the utero-ovarian ligament, and the fallopian tube. The triple pedicles should be individually ligated and transected. There are numerous disposable and reusable surgical instruments that can perform this function.

Visualization of the ureters should be done early in the case, before abrasion of the peritoneum makes identification more difficult. Small incisions can be made in the peritoneum above the ureters to help with later identification, if necessary. The next step is to serially ligate and transect the broad ligament to the level of the isthmus of the uterus. At this level, the bilayers of the broad ligament should be separated into its anterior and posterior leaflets. Careful dissection should be made anteriorly to dissect the bladder away from the lower uterine segment and the cervix. It is imperative to develop the vesicovaginal space to adequately repair the vaginal cuff during the later steps of the surgery. After the bladder is safely dissected away from the isthmus of the uterus, the uterine artery should be further isolated by dissecting the posterior leaf of the broad ligament. Once the uterine artery is isolated, it should be ligated and transected. It is very important to clamp the uterine artery perpendicular to the cervix at the level of the cervical os. This practice, adopted from the widely performed abdominal hysterectomy, will minimize ureteral injury.

Once the uterine artery is transected from the isthmus of the uterus, the next step is to dissect down the cardinal ligament until the lateral fornix of the vagina is reached. It is critical to stay medial to the transected uterine artery and dissect the cardinal ligament parallel to the cervix. Again, this practice will minimize the risk of ureteral injury and also prevent unnecessary blood loss.

After the cardinal ligament is dissected to the lateral fornix of the vagina, the same steps should be taken on the contralateral side. Once this is performed, then the uterus is ready for amputation. The colpotomy can be cumbersome and challenging to perform in many cases because the cervicovaginal junction may be difficult to delineate. However, the use of some of the newer disposable uterine manipulators, which outline the cervicovaginal junction circumferentially, can make this task relatively simple. Once the cervicovaginal junction is clearly identified, then the colpotomy can be performed with monopolar cautery, bipolar cautery hook, or harmonic scalpel. Regardless of energy source used, it is crucial to minimize thermal injury during this step to minimize the risk of vaginal cuff dehiscence.

If the amputated uterus can be extracted from the vagina, then it is advisable to keep the uterus in the vagina to retain pneumoperitoneum if the vaginal cuff is going to be repaired laparoscopically. The vaginal cuff can be repaired by interrupted sutures or by running a continuous suture. Both techniques are acceptable. With both techniques, it is crucial to take at least 1 cm of full thickness purchase of the pubocervical fascia to reapproximate the vaginal cuff. This is only possible by taking the time and diligence to dissect the bladder off of the upper vagina in order to adequately develop the vesicovaginal junction.

10 Operative Considerations

10.1 Types of Uterine Manipulators

Generally, the type of uterine manipulator depends on personal preference due to experience or familiarity of use. Some uterine manipulators are reusable while others are disposable. Many manipulators have cups that clearly delineate the vaginal fornices and thus the cervicovaginal junction. This makes the colpotomy much easier. Some have built-in pneumo-occluder balloons that trap the CO_2 in the abdominal cavity when the colpotomy is made. Others have various mechanisms to allow greater degrees of freedom of movement.

10.2 Choice of Abdominal Entry (Peritoneal Access) Technique

There are three common techniques for entering the abdominal cavity: Hasson open entry, closed entry with a Veress needle, and closed entry with direct optical entry.

The open entry (Hasson) technique is performed by making a periumbilical incision on the skin and dissecting until the fascia is reached. The fascia is then grasped with a Kocher clamp, and the fascia and underlying peritoneum is entered with scissors. Sutures are placed on both sides of the fascia and anchored to the trocar.

The Veress needle technique involves using a hollow-bore needle to directly enter the peritoneal cavity. This is a blind technique that relies on haptic feedback and audible "clicks" as the needle penetrates the fascia and peritoneum. The "clicks" are produced by the recoil of the spring-loaded safety obturator as it traverses the fascia and peritoneum. Intraperitoneal placement is confirmed by the free passage of saline through the needle and low starting intraperitoneal pressure confirmed by the insufflator machine. Once access is confirmed, the abdomen is fully insufflated with carbon dioxide gas.

The direct optical entry technique is performed using specialized optical trocars with a transparent tip. The obturator of the trocar has an opening that allows for direct insertion of the laparoscope. The peritoneal cavity is then entered with direct visualization. The major advantage of this technique compared to the Veress needle technique is lower rates of failed entry (Larobina and Nottle 2005).

The latest meta-analysis in 2012 has concluded that major complications for all entry techniques are similar. There was no advantage of open versus closed entry techniques in reduction of vascular or visceral injury contrary conventional wisdom. There was an increased rate of failed entry with the Veress needle. Lastly, there was quicker entry time with the direct optical entry technique. (Ahmad et al. 2012)

10.3 Placement of Ports

The location for port placement is determined by the size of the uterus, the concern for underlying adhesive disease, the presence of any abdominal wall hernias, and the surgeon's preference. The primary port is usually placed intra- or periumbilically with bilateral secondary ports placed just lateral to the rectus muscles and inferior epigastric vessels. The location of the inferior epigastric vessels is generally delineated by using an imaginary line extending superiorly along the anterior abdominal wall from the insertion of the round ligaments at the inguinal canal. Staying lateral to this imaginary line avoids injury to the inferior epigastric vessels. Transillumination from the peritoneal cavity does not reveal these epigastric vessels but instead reveals superficial vessels in the skin. These superficial vessels may be inadvertently lacerated during port placement leading to superficial hematomas and thus should also be avoided. In cases of suspected abdominopelvic adhesive disease, Palmer's point can be used for the primary port, as described in the previous section.

10.4 Selection of Instruments

With any surgery, the availability and usage of appropriate instruments facilitates the ease,

speed, and safety of surgery. A 0° laparoscope is typically used to start. A 30° laparoscope is recommended for visualization around a large uterine body: anteriorly during the creation of the bladder flap, laterally for access to the uterine vasculature and ligaments, and posteriorly to aid visualization of the cervicovaginal junction during colpotomy. Typically, a vessel-sealing device and a cutting device are needed. There are many devices that perform one or both of these functions, but the advantages and limitations of specific devices are beyond the scope of this chapter. Generally, a bipolar vessel sealer with a cutting feature capable of ligation and transection of the ligaments, vessels, and peritoneal layers and a monopolar electrosurgical device to perform the colpotomy are sufficient. A suction irrigator is necessary for clearing away any blood and to ensure that no uterine or fibroid tissue fragments remain after morcellation. An array of grasping tools, both penetrating and blunt, are also required to manipulate the uterus, adnexa, or bowel. In case of morcellation of a large uterus or in a supracervical hysterectomy, a morcellator is commonly used to facilitate removal of the uterine corpus and cervix, as long as malignancy is not suspected.

10.5 Minimizing Risk of Ureteral Injury

The most common complication in laparoscopic hysterectomy is injury to the urinary tract. The ureters can be easily injured for all types of hysterectomy, especially laparoscopic hysterectomy. Knowledge of the anatomic course of the ureter is vital to avoid direct or indirect injury to the ureter. Injury may occur when ligating and transecting the infundibulopelvic ligaments and vessels, the uterine arteries, the cardinal ligaments, and the uterosacral ligaments. With laparoscopy, visualization of the ureter is much easier due to the magnified optics, illumination, and insufflation of the abdominal cavity. The ureter is commonly identified transperitoneally at the lateral pelvic side wall as it courses inferiorly and medially toward and lateral to the uterosacral ligaments. It can also be located overlying and crossing the bifurcation of the common iliac vessels or at the pelvic brim just lateral to the insertion of the infundibulopelvic ligament and vessels. If scarring of the peritoneum from prior pelvic infection, surgery, or endometriosis is noted, a retroperitoneal entry and dissection starting with the transection of the round ligament will allow identification of the ureter along its course. In rare cases, a complete ureterolysis may be required.

During ligation of the uterine artery, the uterine manipulator cup is pushed in a cephalad direction to create tension at the cervicovaginal junction. This increases the distance between the uterine artery and ipsilateral ureter to minimize direct injury or indirect thermal injury to the ureter. Currently the recommendation by the American Association of Gynecologic Laparoscopists (AAGL) recommends cystourethroscopy after laparoscopic hysterectomy at the surgeon's discretion. However, their recommendation stops short of recommending routine use in all laparoscopic hysterectomy procedures due to insufficient evidence of benefit for detecting all urinary tract injuries. Further discussion of management of ureteral injury is discussed below.

10.6 Minimizing Risk of Bladder Injury

Adequate visualization of the bladder peritoneal fold is necessary, and using a 30° laparoscope may facilitate this. When skeletonizing the uterine artery, the anterior and posterior leaflets of the broad ligament are typically separated with the anterior layer incised medially to create the bladder flap. In the case of adhesions from endometriosis or pelvic infection or scarring from prior surgery (such as a cesarean section), careful attention to the underlying cervical and vaginal vasculature as well as the bladder vascular pillars is necessary to avoid persistent oozing of blood that can obscure the surgical field. One technique to minimize this is to tent the bladder using a grasper or to backfill the bladder with air or saline to demarcate the borders of the bladder dome. Blunt dissection using an atraumatic grasper, a probe, or an electrosurgical instrument can gently

separate the bladder from the anterior lower uterine segment, cervix, and vagina. If scarring is dense, sharp dissection using laparoscopic scissors or careful monopolar coagulation just superior or at the level of the bladder flap will further dissect deeper into the lower uterus or cervix, which can facilitate separation of the bladder adhesion. Lateral transection of the round ligament can also provide access to the bladder flap. Another technique is a posterior approach where the cardinal ligament and uterine vessels are first transected, allowing access to the plane of pubocervical fascia, and thus entry to the vagina is made posteriorly to the scarred bladder adhesion.

Further discussion of management of bladder injury is described below.

10.7 Techniques to Identify the Uterine Artery

Gentle separation of the anterior and posterior leaflets of the broad ligament should allow for skeletonization of the uterine artery. If prior scarring is noted, anatomy may be distorted. Additional techniques to locate the uterine artery include retroperitoneal dissection of the internal iliac artery to locate the origin of the uterine artery. Traction on the medial umbilical fold will identify the origin of the obliterated umbilical vessels from the uterine artery. The ureter can be found directly below this insertion point.

10.8 Approaches to Closure of the Vaginal Cuff

The closure of the vaginal cuff can be done vaginally after removal of the amputated uterus and cervix specimens or before removal of the specimens if the specimen is too large to remove vaginally and morcellation is planned. The closure of the vaginal cuff can also be performed laparoscopically with intracorporeal or extracorporeal knot tying. Deciding which route of closure is based on surgeon experience, preference, and patient factors such as age, parity, and obesity. Extensive electrosurgical desiccation at the cuff site should be avoided. Ideally, at least a 1 cm margin of tissue should be incorporated to minimize cuff dehiscence. Transvaginal closure of the cuff has been shown in retrospective studies to have a lower risk of cuff dehiscence, although this has not been evaluated with randomized prospective studies (Uccella et al. 2012).

10.9 Concomitant Removal of the Fallopian Tubes and/or Ovaries

The risks and benefits for removal of the fallopian tubes and/or ovaries at the time of hysterectomy should be discussed preoperatively with the patient. There are increasingly numerous studies showing that the fallopian tube may be the origin of ovarian, fallopian, and primary peritoneal cancer. Thus, concomitant removal of the fallopian tube at the time of hysterectomy is becoming more common (Przybycin et al. 2010). Removal of the ovaries at the time of hysterectomy depends on the indication of the hysterectomy, age of the patient, and any concomitant adnexal pathology. Without indication for removal, ovaries should be left in situ as numerous studies have shown benefit for morbidity and mortality in retaining the ovaries. (Parker et al. 2013)

11 Complications

11.1 Bladder Injury

If bladder injury is suspected, instillation of the bladder with sterile milk or methylene blue diluted in saline can identify extravasation of colored fluid. A bubble test can also be performed by insufflating the bladder with air after filling the pelvis with saline above the level of the bladder. If there is a bladder injury, then bubbles can be visualized from the injured site. After repair of the bladder, a Foley catheter should be placed for 1–2 weeks to decompress the bladder and facilitate the bladder healing. If the trigone is injured,

careful assessment for ureteral kinking or injury must also be performed following repair.

11.2 Ureteral Injury

Identification and prophylactic measures as described above are key to minimizing ureteral injury. Cystourethroscopy should be performed if ureteral injury is suspected. If ureteral injury is identified, intraoperative consultation with a urologist is recommended in case ureteral stents, reanastomosis, or resection may be necessary. Thermal spread injuries from electrosurgery are insidious and may present 7–10 days after the time of trauma. Awareness of this potential complication and careful attention to nonspecific complaints in the postoperative period are required to make this diagnosis.

11.3 Bowel Injury

Identification of possible bowel injury is the first step to treatment. The type of repair necessary depends on the type of bowel injury. Injuries often arise from laparoscopic instruments, resulting in sharp puncture or thermal damage. Superficial serosal injuries may be oversewn with excellent results. However, repair of enterotomies depends on size of the defect and the location within the gastrointestinal tract. The repair may be done with primary closure or may require a bowel resection with primary reanastomosis. Intraoperative consultation with a general or colorectal surgeon is recommended.

12 Postoperative Management

Most studies show improved recovery with enhanced recovery regimens including early ambulation for prevention of venous thrombotic events and discontinuation of bladder catheterization immediately after surgery or early during the postoperative recovery period to prevent catheter-associated urinary tract infections. Furthermore, early enteral feeding and minimization of overall intravenous fluids to decrease risk of ileus can also expedite recovery (Kalogera et al. 2013).

The decision for same-day discharge or discharge after 1–2 days depends on surgeon comfort level, institutional guidelines, availability of outpatient follow-up, patient comfort, difficulty of the surgery, and types and severity of comorbidities. Studies have shown that same-day discharge can be safe and cost-effective (Khavanin et al. 2013), however at the risk of slightly increased rates of reevaluation within 60 days (4% for outpatient postoperative care vs 3.6% for inpatient) (Khavanin et al. 2013) and risk of decreased reported quality of life at 2 and 4 days post-operation (Kisic-Trope et al. 2011).

12.1 Common Postoperative Complaints

Informing the patient preoperatively of the likely healing process following surgery can often alleviate patient concerns. Most common postoperative complaints can be addressed with expectation management. The patient should be informed of the duration and degree of vaginal spotting or bleeding. Right shoulder pain due to irritation of the phrenic nerve in the right diaphragm from the carbon dioxide gas and blood should also be discussed. The phrenic nerve innervates both the right diaphragm and right shoulder. The patient should be made aware of expected soreness or bruising at the incision sites. Face and upper body swelling due to prolonged Trendelenburg position may also be expected. Subcutaneous emphysema or crepitus can also occur due to insufflation of carbon dioxide gas in the subcutaneous tissue which then tracks along the subcutaneous plane.

13 Conclusion

Laparoscopic hysterectomy is a minimally invasive procedure that is rapidly growing in popularity compared to other routes of hysterectomy. It is important to counsel patients about the risks, alternatives, and benefits inherent to this procedure.

Successful outcomes are associated with surgeon experience, awareness of pitfalls, timely identification of complications, and active postoperative management.

14 Cross-References

- Abdominal Hysterectomy: Indications, Avoiding Complications
- Diagnosis and Management of Delayed Post-Operative Complications in Gynecology: Neuropathy, Wound Complications, Fistulae, Thromboembolism, Pelvic Organ Prolapse, and Cuff complications
- Diagnosis and Management of Immediate Post-Operative Complications in Gynecology: DVT, PE, Bleeding, Infection, Atelectasis, Pneumonia, Abscess
- Gynecologic History and Examination of the Patient
- Management of Abnormal Uterine Bleeding – Later Reproductive Years
- Management of Uterine Fibroids
- Pathology of the Uterine Corpus
- Robotic Surgery in Gynecology: Indications, Advantages, Avoiding Complications
- Vaginal Hysterectomy: Indications, Avoiding Complications

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Management of Abnormal Bleeding in the Adolescent

Julie Jaffray and Kristina Haley

Contents

Abstract

Heavy menstrual bleeding is the most common sign of an acquired or inherited bleeding disorder in females. For many young women, the manifestations of an inherited bleeding disorder do not surface until menarche, which can lead to a delay in diagnosis. Besides heavy menstrual bleeding, patients can have menstrual pain from bleeding into the corpus luteum, bleeding from trauma or procedures, easy bruising, and gastrointestinal bleeding. An undiagnosed bleeding disorder can lead to severe blood loss, chronic iron deficiency, and unnecessary surgical procedures, such as a hysterectomy. Therefore, identifying a possible bleeding disorder in these young women is crucial to allow an initiation of targeted therapy. Management of bleeding will depend on the diagnosis, as well as the severity and bleeding location. Many adolescent females with menorrhagia can be successfully managed with a combination of hormonal control and/or antifibrinolytics. Depending on the diagnosis, treatment can also include coagulation factor replacement, blood product transfusion, as well as specific therapies for acquired bleeding disorders, such as intravenous immune globulin, plasmapheresis, or corticosteroids.

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1 Introduction

As many as 10–15% of premenopausal women have heavy menstrual bleeding (HMB) and account for 15% of all referrals to gynecologists and over 300,000 hysterectomies annually (James et al. 2006). HMB is secondary to an underlying bleeding disorder in up to 20% of premenopausal women, which translates to two to three million American women (James et al. 2006).

Approximately 40% of teenage girls have heavy periods, and anywhere from 10 to 40% of this group have an underlying bleeding disorder.

The most common underlying bleeding disorders are von Willebrand disease and qualitative platelet disorders. On average, there is an average 16-year delay between onset of symptoms and bleeding disorder diagnosis (Kirtava et al. 2004). It is difficult, based on history alone, to determine which girls with heavy periods have an underlying bleeding disorder.

In adolescent women, self-reports of periods as heavy and irregular, as well as greater than four heavy days out of each cycle, were each associated with being diagnosed with a bleeding disorder (Vo et al. 2013).

In adult women, concerning features for an underlying bleeding disorder include periods lasting >7 days, having leaking/soaking, passing large clots, a family history of a bleeding disorder, and a history of iron deficiency (James et al. 2006; James 2010). Additional signs and symptoms of bleeding disorders include frequent and prolonged (>15 min) epistaxis, excessive or spontaneous bruising, gum bleeding not related to dental problems, and excessive or unusual bleeding with surgical or dental procedures.

Bleeding disorders resulting in heavy periods can be due to deficiency or dysfunction at each level of hemostasis: primary hemostasis, secondary hemostasis, or fibrinolysis. Primary hemostatic dysfunction can come in the form of collagen dysfunction (as in Ehlers–Danlos syndrome), quantitative platelet disorders (acquired disorders like immune thrombocytopenia purpura or congenital platelet deficiency as in thrombocytopenia-absent radii or myosin heavy chain 9-related disorders), qualitative platelet disorders (as in Glanzmann's thrombasthenia or Bernard–Soulier syndrome), or in von Willebrand disease. Secondary hemostatic dysfunction is typically associated with deficiencies of one of the coagulation factors, such as female carriers of hemophilia, who are not infrequently symptomatic with heavy periods. The prevalence for bleeding disorders in adolescent and adult women is wide-ranging as symptoms often go unreported, unassessed, or uninvestigated.

Regardless of the cause, diagnosing an underlying bleeding disorder, if one is present, is important in order to guide adjunctive treatments for heavy periods, treat other symptoms associated with the bleeding disorder, plan for surgeries and other procedures, create emergency plans, and connect the patient with a bleeding disorder community. In general, though, treatment of the associated heavy periods is through some form of hormonal control, typically oral contraceptive pills (OCP's) or intrauterine devices (IUDs). Treatment is also aimed at managing associated symptoms, specifically iron deficiency anemia. In this chapter, the role of the hemostatic system and the contributions of deficiencies or dysfunction within the hemostatic system, as well as interventions, will be discussed.

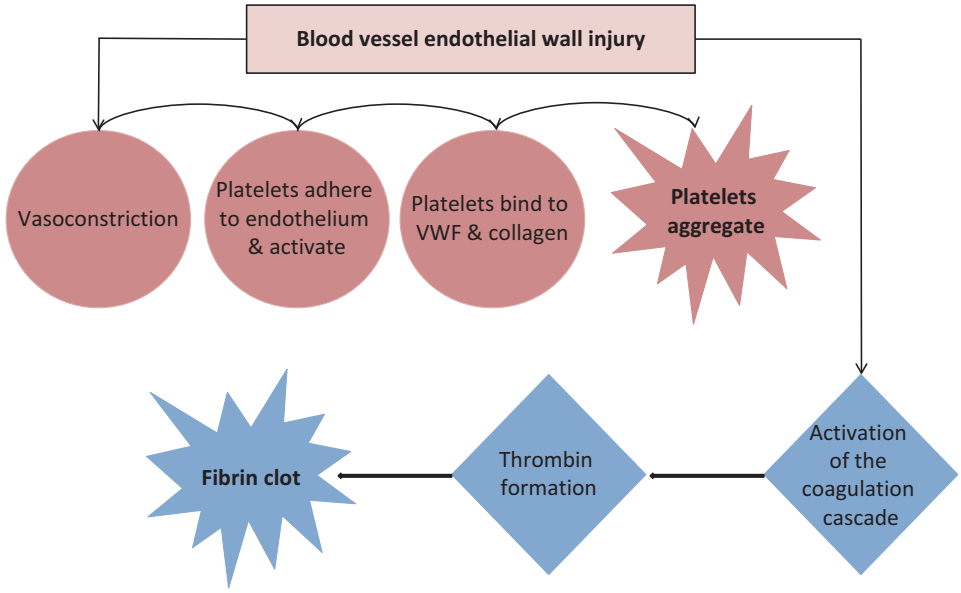

Fig. 1 Key steps in primary and secondary hemostasis, involving activation of platelets and the coagulation cascade to create a stable, cross-linked fibrin clot. *VWF=von Willebrand Factor

2 Overview of Hemostasis

Hemostasis, which is the ability to slow and stop bleeding at the site of injury, is divided into two main components, primary and secondary hemostasis, which occur simultaneously (Fig. 1). Primary hemostasis involves the relationship between the blood vessel wall endothelium, platelets, and von Willebrand factor (VWF). Secondary hemostasis also involves the blood vessel wall, as well as the coagulation proteins, mostly known as factors, and insoluble fibrin.

Primary hemostasis begins with injury to the endothelial lining of blood vessels, which exposes components of the subendothelial matrix to the blood (Gale 2011). These exposed components and receptors allow platelets to adhere to the blood vessel surface and become activated. The platelets bind to VWF and collagen and begin to aggregate to the site of injury. VWF is a multimeric protein which is synthesized in endothelial cells and megakaryocytes and helps with platelet adhesion and activation (Ruggeri 2007). Primary hemostasis also involves the constriction of the blood vessel to enable slowing of blood flow.

Endothelial damage also activates secondary hemostasis by exposing tissue factor and triggering the coagulation cascade (Wolberg and Mast 2012). The coagulation cascade consists of multiple coagulation proteins, or factors, that interact together to form a fibrin clot. These proteins include fibrinogen and factors II, V, VII, VIII, IX, X, XI, and XIII. There are several other factors (factor XII, prekallikrien, and high-molecular-weight kininogen), which are involved in the contact activation system that is currently not considered to be involved in hemostasis (but studies are further exploring their roles, especially with FXII). The most important role of the coagulation cascade is the formation of thrombin (FIIa) at the site of bleeding. Thrombin activates the main catalysts of the cascade, factors V and factor VIII, which generate even more thrombin. This large amount of thrombin then leads to the conversion of another protein, fibrinogen, into fibrin, which forms the structure of the clot. Thrombin also activates factor XIII and thrombin-activatable fibrinolysis inhibitor (TAFI), which help stabilize the fibrin clot. Thrombin also plays a role in promoting primary hemostasis by further

activating platelets to the site of bleeding (Crawley et al. 2007).

3 Inherited Bleeding Disorders

3.1 Von Willebrand Disease

Von Willebrand disease (VWD) results from a quantitative or qualitative defect with the VWF protein. VWF is produced by endothelial cells and by megakaryocytes and undergoes modifications during its synthesis that results in production of VWF arranged in various sizes of multimers. The VWF protein has three functions: (1) protect coagulation factor VIII (FVIII) from degradation, (2) mediate platelet adhesion at sites of vascular injury, and (3) assist in platelet adhesion.

VWD is the most common inherited bleeding disorder, and it is estimated that up to 1% of the entire population is affected by VWD (Rodeghiero et al. 1987). However, only about 1/1,000 are symptomatic.

It is not uncommon for mild VWD to not be diagnosed until adolescence or early adulthood as children may not have bleeding challenges that result in symptoms until they are older. Heavy menstrual bleeding (HMB) is a frequent symptom of VWD, and it is estimated that 5–24% of adult women with HMB have VWD and 3–36% of adolescent women have VWD (Seravalli et al. 2013). Other symptoms of VWD include mucocutaneous bleeding: epistaxis, gum bleeding, hematomas, as well as bleeding with invasive procedures.

A joint statement between the American Academy of Obstetricians and Gynecologists and the American Academy of Pediatrics (AAP) in 2006 advised that healthcare providers should consider the diagnosis of a bleeding disorder, especially VWD, in adolescents with HMB (Khamees et al. 2015).

Recently, the frequency of VWD screening was assessed in an Ohio-based study, and the researchers found that less than a quarter of subjects with severe HMB were screened (Khamees et al. 2015).

There are three main types of VWD. Type 1 VWD is a partial quantitative VWF deficiency and is the most common type of VWD accounting for about 75% of patients with VWD. Type 3 VWD is nearly a complete quantitative VWF deficiency and is the least common type of VWD. Type 2 VWD is further broken down into four subcategories. Type 2A VWD is a qualitative deficiency of VWF-dependent platelet adhesion, with an associated selective deficiency of high-molecular-weight VWF multimers. Type 2B VWD results from a qualitative abnormality in the VWF protein, which results in increased platelet binding, and the VWF deficiency is typically accompanied by thrombocytopenia. Type 2N VWD is characterized by decreased binding affinity of VWF for factor VIII, resulting in a lower than expected factor VIII activity. Type 2M VWD is also a qualitative deficiency of VWF-dependent platelet adhesion, but all VWF multimers are present. VWD is typically an autosomal-dominant disorder, but type 2N and type 3 VWD are inherited in an autosomal recessive manner.

VWD is evaluated through measurement of VWF antigen (a quantitative assessment of VWF protein), measurement of VWF activity (a qualitative assessment of VWF ability to bind platelets most often through the ristocetin activity assay), and measurement of factor VIII activity, which is a qualitative assessment to determine if VWF is adequately protecting factor VIII (Table 1). VWF multimers are measured when trying to differentiate between the various type 2 VWD diagnoses. Levels above 50 IU/dL are generally considered to be within normal limits. Levels above the upper limit of normal are not consistent with a diagnosis of VWD. Stress, estrogen, and acute illness can increase VWF levels. Hypothyroidism can decrease VWF levels. Previous recommendations indicated that patients should be off estrogen-containing contraception prior to testing, but current recommendations do not support this practice as the estrogen content in

Table 1. Laboratory results and inheritance patterns between the types of von Willebrand disease diagnoses

	Type 1 VWD	Type 2A VWD	Type 2B VWD	Type 2M VWD	Type 2N VWD	Type 3 VWD
VWF activity	⇓	⇓	⇓	⇓	⇓	⇓⇓⇓
VWF antigen	⇓	⇓	⇓	⇓	⇓	⇓⇓⇓
Factor VIII activity	N or slight ⇓	N or slight ⇓	N or slight ⇓	N or slight ⇓	⇓	⇓
Multimers	N	⇓ HMWM	⇓ HMWM	N	N	Absent
Platelet count	N	N	⇓	N	N	N
Inheritance	AD	AD or AR	AD	AD or AR	AR	AR

N normal, *HMWM* high-molecular-weight multimer, *AD* autosomal dominant, *AR* autosomal recessive

current oral contraceptives does not significantly impact VWD as to cause a missed diagnosis (Kouides 2008). Individuals with type O blood type have VWF levels that are 20–25% lower than individuals with non-O blood type. The criteria for VWD diagnosis, though, is the same regardless of blood type.

3.2 Hemophilia Carriers

Hemophilia is an inherited x-linked recessive bleeding disorder due to the deficiency of either coagulation factor VIII or IX. Males are generally most affected by the disease due to it being X-linked, and females are known as hemophilia carriers. Persons with hemophilia are classified based on their plasma factor activity level, severe (<1%), moderate (1–5%), or mild (>5–40%) (Blanchette et al. 2014).

Hemophilia carriers typically have factor VIII or IX levels half that of non-hemophilia patients, although levels can range from very low to the lower limit of normal (Plug et al. 2006). Many hemophilia carriers do not experience any excessive bleeding, even during surgeries or postpartum, although some females can have increased bleeding, especially those affected by lyonization. Lyonization is X-inactivation, in which one of the copies of the X chromosome is randomly inactivated leading to lower factor VIII or IX levels. Hemophilia carriers are known as symptomatic carriers when they have bleeding symptoms and will follow the same severity classification based as males, based on their factor levels. Bleeding will usually be mucocutaneous, such as HMB, epistaxis, easy bruising, and gum bleeding, as well as bleeding from trauma, surgical procedures, or postpartum. Males with hemophilia can have mucocutaneous bleeding, as well as bleeding from trauma and surgeries, but bleeding into joints and muscles is the most common site, a problem that is rare in females.

Hemophilia carriers are usually diagnosed after a known family history of hemophilia.

> Factor assays (factor VIII or IX) should be tested on any potential female hemophilia carrier based on family pedigree.

Testing a female with a family history of hemophilia should be performed prior to menarche to avoid any possible severe menstrual bleeding. In a female who has already started her menses, the best time to test factor VIII activity is during the menstrual phase, when the factor level can be at its lowest (Knol et al. 2012). Factor IX activity does not fluctuate with the menstrual cycle, thus testing can be undertaken at any time. Since many carriers will have factor activity levels within the normal range, hemophilia gene mutation analysis is the ideal test to determine carrier status (Peake et al. 1993).

3.3 Rare Factor Deficiencies

Patients can have deficiencies in other coagulation factors such as factor II, V, VII, X, XI, or XIII. Patients with rare factor deficiencies represent 3–5% of all coagulation disorders, with an

incidence of 1 in 500,000 to 1 in 2 million (Acharya et al. 2004; Palla et al. 2015). Patients with factors II, V, VII, X, XI, and XIII deficiency are inherited in an autosomal recessive pattern, and there is a higher incidence of factor XI deficiency in those from Ashkenazi Jewish decent (Seligsohn 2009). Up to 4% of women with HMB have been found to have factor XI deficiency (Kadir et al. 1998). They can present with mucocutaneous bleeding, such as HMB, easy bruising, gastrointestinal bleeding, intracranial bleeding, prolonged bleeding from the umbilical stump, or bleeding after a surgery or trauma. Bleeding phenotype does not correlate well with some rare factor deficiencies, especially factor VII and XI deficiency (Mariani and Bernardi 2009; Seligsohn 2009).

Diagnosing rare factor deficiencies should begin with a PT and aPTT. An isolated prolongation of the PT is seen with factor VII deficiency, and an isolated prolongation of the aPTT is seen with factor XI deficiency (as well as factor VIII and IX deficiency, which was discussed earlier). Patients with factor II, V, or X deficiency will result in a prolongation of both the PT and aPTT. When a specific factor deficiency is suspected, confirmatory factor-specific assays should be performed. The PT and aPTT will be normal in those with factor XIII deficiency; thus, when suspected, a quantitative factor XIII assay should be sent.

3.4 Disorders of Fibrinolysis

Fibrinogen is converted to fibrin and provides the structural material for a blood clot during secondary hemostasis, as discussed above. Patients with disorders of fibrinolysis can either have decreased or lack of fibrinogen levels (hypofibrinogenemia, afibrinogenemia) or a dysfunctional fibrinogen (dysfibrinogenemia). Afibrinogenemia is inherited in an autosomal recessive pattern, where the heterozygous form is hypofibrinogenemia. Patients with disorders of fibrinolysis can present with intracranial bleeding or mucocutaneous bleeding, such as HMB, but will generally present earlier in life prior to menses (Acharya and Dimichele 2008). Patients can be diagnosed with hypo- or afibrinogenemia with a prolonged PT and aPTT. Confirmatory testing is a functional or antigenic fibrinogen assay.

3.5 Inherited Platelet Disorders

Platelets are tiny, cellular fragments that undergo a complex series of changes in response to bleeding, resulting in the initial cessation of blood flow from an injured area (primary hemostasis). As described previously, hemostasis is achieved through a series of coordinated events involving platelet-vessel, platelet-platelet, and platelet-protein interactions. These interactions occur in blood vessels under the shear stress of blood flow. Platelet disorders typically result in mucocutaneous bleeding, including epistaxis, gum bleeding, bruising, and HMB, and platelet dysfunction is found in 3–44% of adolescents with HMB (Seravalli). Platelet disorders can be secondary to qualitative or quantitative defects and can be acquired or inherited. In the adolescent population, the most common acquired platelet disorder is immune thrombocytopenia purpura (ITP). This section will focus on inherited disorders of platelet function and/or number; however, similar symptoms are present in adolescent women with ITP (see section on acquired bleeding disorders below).

Inherited platelet function disorders include a heterogeneous group of disorders. The most well-known platelet disorders are some of the rarer disorders, such as Bernard–Soulier syndrome (BSS) and Glanzmann thrombasthenia (GT). BSS results from a deficiency or defect in the platelet glycoprotein 1b, which impairs platelet binding to VWF. It is extremely rare, and only about 100 cases have been reported in the literature (Israels et al. 2010). GT is a defect in the platelet glycoprotein IIb/IIIa, the glycoprotein that mediates platelet-platelet aggregation. GT is also a rare disorder and is inherited in an autosomal recessive pattern (Israels et al. 2010). The mucocutaneous bleeding in GT can be severe, and menorrhagia and postpartum hemorrhage can be life-threatening. Other platelet disorders

include disorders of platelet granule secretion, platelet signal transduction, and platelet receptor defects. These disorders do not all have specific names but result in characteristic patterns on available platelet function testing. Both BSS and GT result in mucocutaneous bleeding present in early childhood; however, the more common and milder platelet disorders typically present in adolescents and adulthood following menarche and other bleeding challenges.

The best available test for diagnosing platelet disorders is platelet aggregometry. This testing method is difficult to perform, requires large volumes of blood, and does not adequately assess the steps prior to aggregation, such as platelet-vessel interactions, or the effects of flowing blood (Pai and Hayward 2009; Israels et al. 2011). As a result, platelet function disorders are challenging to diagnose, and patients presenting with mucocutaneous bleeding frequently go undiagnosed (James et al. 2006; Kouides 2008). The incidence of platelet disorders in adolescents is wide ranging, from 2% to 46%, but it is suspected that the true incidence of platelet function defects is unknown and that many patients presenting with mucocutaneous bleeding have platelet disorders that cannot be diagnosed with currently available tests (Philipp et al. 2011; Sokkary et al. 2012; Mills et al. 2014).

3.6 Connective Tissue Disorders

Disorders of the vessel wall or with the subendothelial matrix, which may affect platelet adhesion, can also cause menorrhagia (van Ommen and Peters 2012; Vo et al. 2013). Hereditary hemorrhagic telangiectasia (HHT) and Ehlers–Danlos syndrome (EDS) have been associated with HMB. Careful physical examination for telangiectasias (for HHT) or for joint or skin laxity (for EDS) can be helpful in the evaluation of an adolescent with HMB. The Beighton score, a quick physical assessment of joint laxity, can be easily incorporated into the physical exam. A score of 4 or higher is concerning for EDS and warrants further work up. The treatment of HMB in EDS is similar to other hemostatic disorders, primarily with hormonal interventions, IUD, or antifibrinolytics.

4 Acquired Bleeding Disorders

4.1 Immune Thrombocytopenia Purpura

Immune thrombocytopenia purpura (ITP) is an isolated thrombocytopenia (peripheral blood count $<100 \times 10^9$) in patients without other causes or disorders of thrombocytopenia (Rodeghiero et al. 2009). The pathogenesis is thought to be immune-mediated destruction against one's own platelets and megakaryocytes (Cooper and Bussel 2006). The exact etiology of the immune-mediated destruction is unknown but can occur secondary to a viral infection or some vaccinations. In children, ITP is usually a benign disorder that is self-limited and generally resolves prior to 12 months. In adolescents, ITP may have more of a chronic course, and other autoimmune diseases should be considered (British Committee for Standards in Haematology General Haematology Task 2003).

> Mucocutaneous bleeding is the hallmark of ITP, which includes HMB, epistaxis, easy bruising, and gastrointestinal bleeding.

Intracranial bleeding can also occur, but very rarely, with an estimated incidence of 0.2%–0.8% (Psaila et al. 2009). Laboratory assessment should include a complete blood count (CBC) with differential to evaluate all blood cell lines, reticulocyte count, and direct antibody assessment to determine Rh blood antigen status. Patients with ITP will normally have an isolated thrombocytopenia, unless their bleeding has led to iron deficiency anemia. Adolescents with ITP should also have a preliminary rheumatology and immunology work-up including immunoglobulin levels, antinuclear antibody (ANA), complement levels, and a complete metabolic panel (CMP) to evaluate liver and renal function.

Treatment based on platelet count alone remains controversial, and pharmacological treatment options to increase the platelet count and decrease the immune destruction are not always successful, and in many circumstances, the effect is not long lasting. Many pediatric centers are opting toward an observational approach for patients with ITP, regardless of their platelet count (Witmer et al. 2016). Specific pharmacological treatment options include intravenous immune globulin (IVIG), corticosteroids, anti-D immunoglobulin (only if Rh blood antigen positive), rituximab, or splenectomy. Adolescents with HMB can be treated with one of these options in combination with specific treatments for menstrual bleeding as described in the treatment/management section.

4.2 Thrombotic Thrombocytopenia Purpura

Thrombotic thrombocytopenia purpura (TTP) is a serious and life-threatening disorder that leads to microangiopathic hemolytic anemia, thrombocytopenia, and neurological abnormalities. TTP can be acquired or congenital and leads to a deficiency of ADAMTS13, which is responsible for cleaving VWF multimers (Fujikawa et al. 2001). The ultra-large VWF multimers can cause excessive platelet aggregation and thrombosis. The acquired form is due to autoantibodies targeted against ADAMTS13, and the congenital form is due to mutations in the ADAMTS13 gene, leading to decreased production of ADAMTS13 (Levy et al. 2001). Luckily, TTP is very rare in the adolescent population, but can lead to severe mucocutaneous bleeding secondary to the thrombocytopenia.

When TTP is suspected, patients should have a CBC, with peripheral smear review reticulocyte count, CMP, as well as testing for ADAMTS13 activity and inhibitor levels. Until the thrombocytopenia resolves, adolescents with HMB can be treated with therapies listed in the treatment/management section of this chapter. Specific treatment for TTP involves plasma exchange to replace the ADAMTS13 and corticosteroids to target the autoimmune aspect of the disease.

4.3 Liver and Renal Failure

The liver is responsible for the synthesis of most pro- and anticoagulant proteins (except VWF), as well as the synthesis of thrombopoietin, the hormone that promotes platelet production. Therefore, a disruption in liver function can have a large impact on a person's coagulation and cause both hemorrhage and thrombosis. Adolescents with liver disease can present with HMB, extensive bruising, bleeding from blood draws, bleeding from peripheral or central intravenous catheters, intracranial bleeding, or bleeding from invasive procedures. Diseases that lead to liver failure in adolescents include drugs/toxins, viruses, metabolic disorders, and autoimmune hepatitis (Dhawan 2012). Coagulation testing abnormalities that are seen with liver failure are an elevated PT, aPTT, and d-dimer, decreased fibrinogen activity, and decreased platelet count.

Treatment should be targeted toward the underlying etiology in conjunction with specific therapies for bleeding. Treatment for bleeding in liver failure can be difficult due to the risk of thrombosis and fluid overload. Fresh frozen plasma (FFP) can be used, since it contains all coagulation factors as well as cryoprecipitate to replace fibrinogen (Youssef et al. 2003). Prothrombin complex concentrates (PCCs) are lower in volume than FFP and can help replace factors II, VII, IX, and X. Specific therapies for menorrhagia discussed in the treatment/management section should be used with caution, as with all treatment in liver disease due to the risk of thrombosis.

> Patients with end-stage renal disease have bleeding secondary to platelet dysfunction due to uremia (Escolar et al. 2005).

Uremia can affect platelet granule secretion, which leads to platelet activation and aggregation, as well as affecting platelet adhesion to the vascular endothelial wall with the help of fibrinogen and VWF. Platelet function can temporarily improve after dialysis removes toxins such as urea. Patients can have mucocutaneous bleeding such as HMB,

easy bruising, or gum bleeding. Treatment of bleeding in patients with end-stage renal disease includes dialysis, which removes the urea, desmopressin (DDAVP) which releases VWF, and cryoprecipitate (Kaw and Malhotra 2006).

5 Laboratory Evaluation

It is difficult to determine what menstrual symptoms warrant further work-up as patients have difficulty quantifying blood loss. Further, adolescents who have not had many menstrual periods may not have a reference point for normal due to their lack of experience, especially if their mothers, aunts, or siblings also have heavy periods. A few tools have been developed to assess menstrual blood loss with regard to the presence or absence of an underlying bleeding disorder. Bleeding assessment tools (BATs) are excellent at capturing bleeding symptoms but unfortunately are frequently too long to administer in a clinic visit. The pictorial blood assessment chart (PBAC) is a tool that can be employed to assess for HMB (Higham et al. 1990, 2016). A total score of greater than 100 is concerning for an underlying bleeding disorder as a cause for HMB. Further, the Phillip score can be employed to further assess a patient (Philipp et al. 2011). A bleeding disorder should be pursued if one of the following four criteria of the Phillip score is met: duration of menses more than 7 days and either flooding or impairment of daily activities, a history of treatment for anemia, a family history of a bleeding disorder, or a history of bleeding with tooth extraction, delivery or miscarriage, or surgery. These two tools, the PBAC and the Phillips tool, have been validated in the adult population but not in the adolescent population.

For a laboratory evaluation, a few screening labs can be employed by the gynecologist or primary care physician (Table 2). A CBC will allow for assessment of platelet count as well as for the presence of anemia. The secondary hemostatic system should be screened for deficiencies with a PT, aPTT, and fibrinogen. A VWD panel should also be obtained to screen for VWD, including a VWF/antigen, VWF/activity, and factor VIII activity. Abnormally low values or borderline values should be repeated given the variability in laboratory assessments. Screening for platelet dysfunction is difficult due to lack of sensitive and specific platelet disorder screening assays. The platelet function analyzer-100 (PFA-100) was created as a screen for platelet function disorders but unfortunately is not sensitive or specific enough to use as a screening test. If the CBC, PT, aPTT, fibrinogen, and VWD panel are normal and the patient is still experiencing symptoms, then referral to a hematologist is warranted for further work up. Because hypothyroidism can affect VWF levels and affect menses, screening for thyroid dysfunction may also be prudent to add in the evaluation.

A CBC can be employed to screen for anemia. However, there are a significant proportion of young women with HMB with iron deficiency without anemia.

> Thus, if symptoms of anemia are present such as fatigue, difficulty concentrating, restless legs, or pica, iron studies should be obtained (ferritin, total iron binding capacity, serum iron, and percent transferrin saturation).

6 Treatment/Management

From a gynecologic standpoint, oral contraceptives are often the first line in controlling HMB as they reduce menstrual blood loss. The levonorgestrel-releasing intrauterine device (IUD) is also a very effective intervention and has been shown to result in a significant reduction in PBAC scores as well as an increase in hemoglobin concentration. The NHLBI guidelines state that the first choice of therapy for HMB in patients with bleeding disorders should be combined oral contraceptives followed by the IUD (O'Brien 2012).

Specific treatment options for patients with bleeding disorders include DDAVP (1-desamino-8-D-arginine vasopressin), antifibrinolytic therapies, and factor concentrates. DDAVP stimulates

Table 2 Overview of appropriate laboratory tests and referral recommendations for adolescents with heavy menstrual bleeding

Stage of hemostasis being assessed	Test	Abnormal result suggesting bleeding disorder	Follow-up
Primary	CBC	Thrombocytopenia	Referral to hematology for evaluation of thrombocytopenia, obtain iron studies if not completed for anemia
		Anemia	
Primary	VWD panel (VWF/Ag, VWF/RCo, FVIII act)	VWF/Ag <40%	Repeat VWD panel
		VWF/RCo <40%	Referral to hematology for further evaluation
		FVIII Act <60%	
Secondary	PT	Elevated PT	Mixing study
			Factor VII activity
			Referral to hematology
Secondary	aPTT	Elevated PTT	Mixing study
			Factor VIII, IX, XI, and XII activities
			Referral to hematology
Secondary	Fibrinogen	Low fibrinogen	Thrombin time
			Referral to hematology

CBC complete blood count, *VWD* von Willebrand disease, *VWF/Ag* von Willebrand factor antigen, *VWF/RCo* VWF activity, *FVIII Act* factor VIII activity, *PT* prothrombin time, *aPTT* partial thromboplastin time

the release of stored VWF from Weibel–Palade bodies in endothelial cells. It is available in both intravenous and intranasal forms, but is only effective for 48–72 h. DDAVP is commonly used to treat bleeding associated with VWF, but it is also effective in treating bleeding in patients with some platelet dysfunction disorders, likely by increasing platelet adhesion due to increased VWF levels. Patient with type 2 VWD have a variable response as the released VWF is likely dysfunctional. DDAVP is not effective in patients with type 3 VWD or the platelet dysfunction diseases, GT or BSS. A DDAVP stimulation test should be performed prior to its use in order to determine an individual's response. DDAVP's primary side effect is increased water retention and secondary hyponatremia, thus fluid guidelines should be provided to patients.

The antifibrinolytic therapies include aminocaproic acid and tranexamic acid. These two agents inhibit fibrinolysis and allow for clot stabilization. They are particularly useful hemostatic agents in the setting of mucocutaneous bleeding (O'Brien 2012). Aminocaproic acid is available in tablet and liquid forms, allowing for use in patients who are unable to swallow pills. Tranexamic acid is generally better tolerated, though, with regard to gastrointestinal upset and headaches. The antifibrinolytics are effective treatments in all bleeding disorder types.

Factor concentrates contain specific clotting factors for VWD or factor deficiencies. While factor concentrates are rarely used to treat HMB, in acute menorrhagia unresponsive to antifibrinolytics or estrogen therapies, factor concentrates may be necessary. These concentrates must be administered intravenously (IV), and the concentrates that are currently available in the United States include VWF, fibrinogen, as well as factors VII, VIII, IX, X, and XIII. Not all hospitals carry factor concentrates so it is encouraged that patients with VWD or factor deficiencies have at least one life-saving dose of factor available to them at home. Patients can also receive fresh frozen plasma (any factor deficiency), cryoprecipitate (fibrinogen, FXIII deficiency), or prothrombin complex concentrates (factors II, VII, IX, and X deficiency) if specific factor replacement is unavailable. Fresh frozen plasma is the only current replacement for factor V and XI deficiency in the USA. For patients with platelet disorders, platelet transfusions or recombinant

factor VIIa may be necessary to control bleeding, particularly at times of surgery, childbirth, or dental work (Young et al. 2009).

As indicated above, iron deficiency with and without anemia is common in adolescents with HMB.

If iron deficiency is diagnosed, replacement iron therapy should be initiated. Oral iron with ferrous sulfate 325 mg (65 mg elemental iron) daily is often effective. At least 3 months of therapy are typically required in order to replenish iron stores. However, if HMB is ongoing, it may take longer to replenish iron losses. Continuing iron therapy 3 months beyond improvement of HMB is often an effective strategy. Iron supplements should be taken with vitamin C to increase absorption, and they should not be taken with milk or teas as these decrease absorption. Gastrointestinal side effects such as abdominal pain, nausea, and constipation are common. If oral iron is not tolerated, IV iron should be considered. There are several formulations of IV iron available, with improved side effect profiles compared to previous IV iron preparations. If iron stores do not improve following improvement of menstrual losses, other sources of blood loss should be investigated. Iron deficiency and iron deficiency anemia have been associated with lower academic success and impaired physical activity; thus, it is imperative to address this issue in adolescent females (Rae et al. 2013).

6.1 Medications to Avoid

In patients with bleeding disorders, medications that affect hemostatic function should be avoided.

The nonsteroidal anti-inflammatory medications (NSAIDs) affect platelet function and may exacerbate an underlying bleeding disorder.

NSAIDs are found in a variety of medications, and patients with bleeding disorders should be instructed on reading labels in order to avoid taking one of these medications unintentionally. While NSAIDS are generally not recommended for patients with bleeding disorders, their beneficial effect on dysmenorrhea and menorrhagia requires additional consideration. NSAIDs inhibit cyclo-oxygenase and reduce the production of prostaglandins and thromboxanes. In women with menorrhagia, prostaglandins are elevated and result in vasodilation, which likely results in increased menstrual losses. As NSAIDs block prostaglandin production, they can decrease menstrual blood loss through this mechanism. Thus, NSAIDs may be an effective tool to decrease menstrual losses in adolescents with HMB and bleeding disorders, particularly if their primary symptom is HMB. The risks and benefits of NSAIDs should be discussed with the patient and her parent or guardian, and if instituted, careful monitoring of bleeding symptoms should be undertaken (O'Brien 2012).

The selective serotonin reuptake inhibitors (SSRIs) inhibit the serotonin reuptake transporter 5-HTT and are a common medication employed in the management of depression and anxiety. Serotonin is a platelet agonist, and 5-HTT is present on the platelet surface. Platelets do not make their own serotonin and are dependent upon 5-HTT for their serotonin content. There have been reports of bleeding in patients on SSRIs, including gastrointestinal and perioperative bleeding. The effect appears to be modest and more common in older patients. As SSRIs are a very effective tool in the management of mental health disorders, the bleeding risk should be balanced with the therapeutic benefit (Konkle 2011).

7 Conclusion

Abnormal bleeding in the adolescent can result in severe anemia and inappropriate procedures if not diagnosed and treated in a timely fashion. Causes

of bleeding in adolescents range from inherited disorders such as factor deficiencies and platelet dysfunction to acquired problems such as ITP and liver failure.

> Patients with HMB and a history of other mucocutaneous bleeding, such as epistaxis, gum bleeding, easy bruising, or gastrointestinal bleeding, should be evaluated for a bleeding disorder.

Diagnosing a bleeding disorder can be difficult due to issues with procurement of the blood sample and interpretation of the laboratory results. Blood flow into collection tubes must be free-flowing in order for the coagulation system not to be activated. The blood samples are also sensitive to heat inactivation/cold inactivation and delay in centrifugation or processing. Interpretation of coagulation test results is also difficult; thus, any second-tier testing and analysis are best done by a trained hematologist. A framework has been provided to help diagnose and treat adolescents who present with abnormal bleeding (Fig. 2). This algorithm should help primary care physicians and gynecologists begin the work-up for a bleeding disorder as well as guide any emergently needed treatment. Most adolescents with HMB and an undiagnosed bleeding disorder can be treated safely with standard of care measures until a diagnosis has been established. While HMB may be the primary or presenting symptom of many bleeding disorders, it is important that the patient be referred to a hematologist as soon as a bleeding disorder is suspected in order to help manage symptoms as well as to create hemostatic plans for emergencies or invasive procedures.

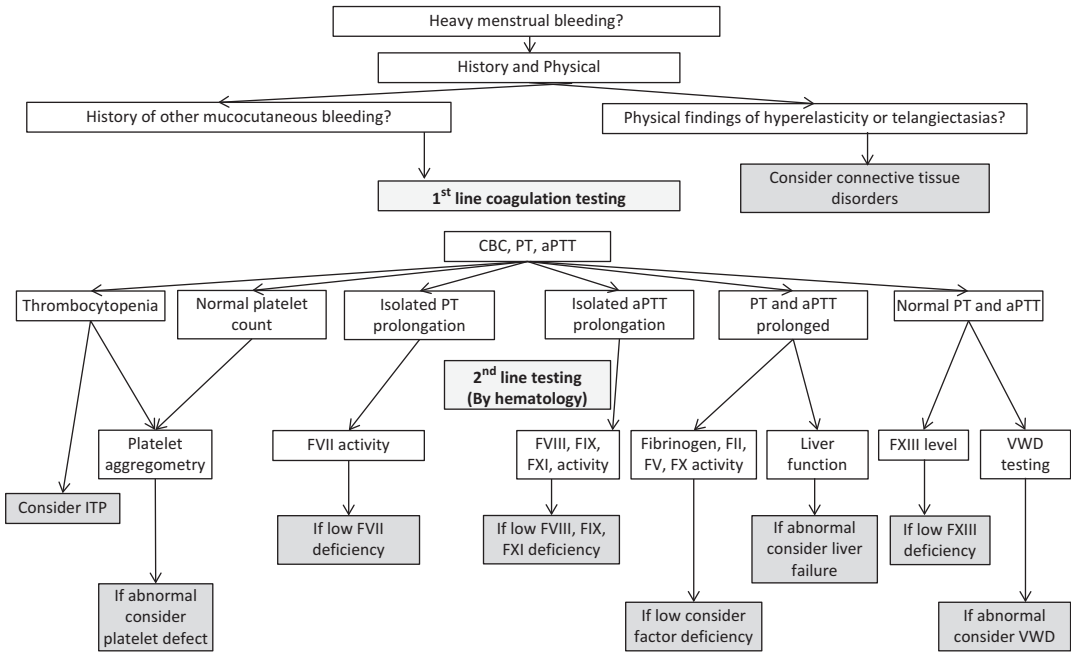

Fig. 2 Coagulation testing algorithm and diagnostic considerations for adolescents with heavy menstrual bleeding and the concern for an underlying bleeding disorder. *CBC=Complete blood count, PT=prothrombin time, aPTT=activated thromboplastin time, FVII=Factor VII, FVIII=Factor VIII, FIX=Factor IX, FXI=Factor XI, FII=Factor II, FV=Factor V, FX=Factor X, FXIII=Factor XIII, VWD=von Willebrand disease, ITP=Immune thrombocytopenia purpura

8 Cross-References

▶ Workup and Management of Polycystic Ovary Syndrome

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Management of Pelvic Pain

Donna Shoupe

Contents

Abstract

There are numerous etiologies of pelvic pain in women. These include pain of gynecologic, urologic, gastrointestinal, musculoskeletal and vascular origins. The etiologies range from infections, pregnancy, neoplasms, torsion, structures, scarring, inflammation, fibroids, endometriosis, kidney stones, irritable bowel syndrome, prolapse, painful vessels, or menstrual cramps. Pelvic pain is divided into acute, chronic, or recurrent pain. While there can be significant overlap, the initial approach in establishing the etiology and management differs among these groups. A careful history and physical exam followed up with appropriate laboratory and diagnostic studies continually narrow the list of potential diagnoses. Quickly ruling out critical or life-threating conditions is particularly important in women presenting with acute pelvic pain.

Keywords

Acute pelvic pain • Chronic pelvic pain • Pelvic pain • Recurrent pelvic pain • Endometriosis • Myofascial pain syndrome • Dysmenorrhea • Adnexal pain • Trigger points • Leiomyomata

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1 Introduction

Pelvic pain in women is divided into acute, chronic, or recurrent pain. While there can be significant overlap, the initial approach in establishing the etiology and management differs among these groups. Generally, pain for more than 3–6 months in duration that is primarily located in the pelvic area is chronic pelvic pain (Howard 2000). Women with chronic pelvic pain may also have recurrent pain with intercourse or pain that is timed around the menstrual cycle. The origin of pelvic pain may be due to a variety of etiologies including gynecologic, gastrointestinal, urologic, musculoskeletal, vascular, and metabolic disorders. A careful history and physical exam followed up with appropriate laboratory and diagnostic studies continually narrow the list of potential diagnoses. Quickly ruling out critical or life-threating conditions is particularly important in women presenting with acute pelvic pain.

2 Acute Pelvic Pain

The most common problems associated with acute pelvic pain in women are shown in Table 1. Acute pain may be due to somatic, visceral, or neurogenic origin or from a combination of these. Somatic pain [body wall] may originate from the skin, ligaments, muscles, bones, or joints. Somatic sensory neurons respond to touch, temperature, or injury. Somatic pain is usually located over the affected area and often directs the provider to the correct etiology and diagnosis.

Visceral pain [viscus or organ] occurs when a viscus or internal organ is damaged, injured, or stretched. Visceral receptors are located within the walls of hollow viscera and serosal surfaces and within the mesentery. Injury to a viscus often causes nausea, vomiting, or sweating. Localizing the site of visceral injury can be difficult as there is significant overlap of nerve pathways and the pain can be "referred" into unrelated areas of the body. Visceral pain is often characterized as a dull, deep poorly defined sensation in a poorly defined area. Visceral pain can be accompanied by sweating, nausea or vomiting, pallor, diarrhea, or fever. Many women present with both visceral and somatic pain.

Neurogenic pain is injury to sensory nerves. Neurogenic pain may be due to herpes zoster, tumors, syphilis, disk disease, injury, multiple sclerosis, other infections or arthritis.

Table 1 Common problems associated with acute pelvic pain in women. See Table 2 for common problems associated with chronic or recurrent pelvic pain as these conditions may on occasion present as acute pelvic pain

Gynecological	Pelvic inflammatory disease	Urologic	Kidney/ureteral stone
	Ectopic pregnancy, spontaneous or induced abortion		Cystitis, pyelonephritis
	Hemorrhage [leaking], torsion or rupture of ovarian neoplasm or functional cyst, paratubal cyst, fallopian tube	Other	Constipation, diarrhea, bowel obstruction, diverticulitis
	Trauma		Hernia
	Degeneration, torsion, or aborting fibroid		Musculoskeletal particularly hip injury, degeneration
	Endometritis		Skin: shingles, infection
	Ovarian hyperstimulation	Obstetrics	Labor, uterine rupture, abruption
	Cervical stenosis		Ovarian vein thrombosis, other thrombosis
	Complications of an IUD		Diastasis of pubic symphysis
	Vaginal atrophy, vaginitis		Endometritis, retained products of conception

3 Evaluation and Management

The first priority in addressing acute pelvic pain is to rule out any life-threatening condition that may mandate immediate medications or surgery. Severe acute pain, hypotension, tachycardia, fever, positive pregnancy test, marked abdominal distention, pronounced guarding, rebound, rigid abdominal wall, or postural hypotension are factors that providers should address immediately.

The history includes:

- **Age, gravity, and parity**
  - Reproductive-aged women: last menstrual period and menstrual history, missed menstrual period, contraceptive history, sexual activity, "have you taken a pregnancy test?"
    - OB history: prior ectopic, caesarian section
  - Postmenopausal women: bleeding, changes in bowel function, meds, medical problems
- **Duration** of symptoms, sudden or gradual onset
- **Location** of symptoms
- **Intensity** of symptoms: 10-point scale (Fauconnier et al. 2009)
- **Character** of symptoms
  - Sharp, dull, crampy, colicky, cyclic, waxing, pinching, cutting, throbbing, burning, pulling
- **Mitigating, aggravating factors**
  - Pain meds used, OTC meds used, change with positioning or walking, sex, menses, bleeding, "what makes it worse or better?"
- **Other symptoms**: bowel function changes, nausea, vomiting, urinary complaints [frequency, dysuria], effect on sleep
- **Past medical history/records**
  - Previous diagnoses of related conditions, previous workup: ultrasound results, previous STDs, current meds, results of last Pap smear
- **Prior surgery**: tubal surgery, bowel surgery, recent surgery
- **Social history:** recent trauma, substance abuse, domestic violence, high-risk sexual behavior

A detailed history can often narrow the diagnosis and direct the provider to the important parts of the physical exam and appropriate diagnostic studies. Important parts of the physical exam include:

- **General**: acute distress, guarding in pain, changes in orientation
- **Vital signs**: hypotension, tachycardia, or elevated temp
- **Abdominal exam**: presence of bowel sounds, guarding, rebound, area of pain, distention, skin changes, previous surgical scars, hernias
  - Identify areas of tenderness to palpation and masses.
- **Pelvic exam**:
  - External exam: erythema, ulcers, discharge, rashes, swelling, discoloration, palpate, and inspect the Bartholin, skene, and urethra
  - Vaginal exam: mucosa erythema, discharge, lacerations, mass, foreign body, bleeding, ulcerations, tenderness, cystocele, rectocele
  - Cervical os: discharge, bleeding, polyp, myoma
  - Bimanual:
    - Uterus, size, shape, consistency, tenderness, asymmetries, prolapse
    - Adnexal masses, tenderness, fixation
    - Pain on cervical motion
    - Pain over bladder or pain on bladder palpation
  - Rectovaginal exam: masses or fullness in rectovaginal septum, cul-de-sac, or rectum, uterosacral nodules

Following an accurate history and physical exam, a narrowed differential diagnosis can direct further laboratory and diagnostic testing. *Management of conditions is included below.*

- Reproductive-aged women with **acute** pelvic pain
  - Pregnancy test and CBC
    - If positive pregnancy test, ultrasound is used to identify the location of pregnancy and/or viability.

  - If associated with anemia and/or pain on cervical motion, it is important to rule out ectopic pregnancy: *treatment is medical [methotrexate] or surgical [laparoscopy or [if acute heavy bleeding, unstable patient] laparotomy], expectant management, and RhoGAM if needed.*
  - The incidence of interstitial pregnancy is rising. Treatment also includes methotrexate [most widely used nonsurgical treatment, systemic or local injection], laparoscopic or laparotomy, expectant management, and RhoGAM if needed (Moawad et al. 2009).
  - Open cervical ostia consistent with inevitable, complete, or incomplete spontaneous miscarriage: *treatment is medical, surgical evacuation [D & C], expectant management, and RhoGAM if needed.*
- Elevated white cell count, usually bilateral adnexal pain, and fever is consistent with pelvic inflammatory disease: *immediate antibiotic treatment is important:*
  - Tubo-ovarian masses are a severe form of PID and are treated with multiple IV antibiotics, possible drainage of masses by radiology or surgery, and rarely surgical removal.
- Elevated white cell count, usually unilateral right lower quadrant pain and fever may indicate appendicitis; differentiate with abdominal/pelvic MRI, CT, ultrasound, or diagnostic laparoscopy:

- Women with enlarged uterus or adnexal masses on exam
  - Pelvic ultrasound or MRI, CT
    - Fibroids: treatment expectant management, myomectomy, or hysterectomy.
      - Perimenopausal fibroid degeneration *may not need surgical intervention.*
    - Ovarian functional cysts, endometrioma, dermoid, cystadenoma, or other neoplasms may undergo torsion or leakage.
      - Pain may come and go, increased with movement.
      - Peritoneal irritation due to leakage of material from a cyst may cause distension, tenderness, and localized rebound.
      - Bleeding corpus luteum can on occasion be associated with frank hemorrhage and hemoperitoneum and on rare occasions, hypovolemic sh0ck. *Treatment includes laparoscopy or laparotomy and control of bleeding.*
      - Ultrasound can show blood flow and can rule out ovarian torsion.
      - If torsion of ovary is expected, immediate laparoscopy is indicated to save the ovary from necrosis.
    - Tubo-ovarian abscesses [multiple antibiotic coverage, consider CT-guided drainage if nonresponsive, rarely surgical intervention/removal needed]
    - Position and presence of IUD noted [*removal of malpositioned IUD]*
- Women, particularly >50 years, with GI-related complaints and/or exam findings
  - MRI, CT, pelvic, or renal ultrasound, colonoscopy, testing blood in stool
    - Diverticulitis [special diet, referral to GI or primary care]
    - Dilated loops of bowel, bowel obstruction
    - [immediate GI consult]
    - Chronic constipation, IBS [*primary care, GI consult*]
- Women with dysuria, frequency, urgency, bladder pain
  - Urinalysis, culture, and sensitivity
    - UTI, cystitis, antibiotic treatment, interstitial cystitis [NSAID, tricyclic antidepressants, antihistamines, Elmiron, consider GYN/ urology consult, bladder infusions]
    - With flank, back or side pain, and fever, consider pyelonephritis
- Women with severe unilateral pelvic pain and negative pregnancy test

  - Pelvic ultrasound, MRI, or CT
    - Sudden, severe pelvic pain may be kidney stone passing: treatment includes wait and watch, destruction of stone, or surgical intervention by urology.
      - Urinalysis usually positive for hematuria, confirmed with KUB, ultrasound, IVP
    - Urinary tract obstruction [*urology consult]*
- Women with changes in bowel function, chronic constipation.
  - Check for blood in stool, consider GI referral, colonoscopy.
  - Older women should be evaluated for diverticular disease and *appropriate referral.*
  - Umbilical pain followed by right lower pelvic pain, usually high white count and fever, and negative pregnancy test consistent with appendicitis [can be associated with cervical motion pain] *[refer to GI*].
- Acute exacerbation of chronic pelvic pain, chronic dysmenorrhea, and dyspareunia, with/without adnexal mass [endometrioma] may be endometriosis: *treatments include oral contraceptive pills, Mirena IUD*, gonadotropin agonists ± add-back, and *surgical treatment*.
- Postmenopausal women with pain and bleeding, imaging studies, and endometrial sampling.

Most women with acute pelvic pain, normal laboratory, vital signs, imaging studies, and physical exam will experience resolution of symptoms without surgical intervention. Laparoscopy has an important role in the management of ovarian torsion and ectopic pregnancy and in some instances where there is no clear diagnosis.

4 Chronic Pelvic Pain

Chronic pelvic pain is defined as severe enough pain to cause functional disability for at least 6-month duration occurring in the abdomen below the umbilicus. Chronic pelvic pain may lead to disability, marital problems, loss of job, suffering, years of pain medications, and/or extensive surgical procedures. It is important that the healthcare provider complete an initial extensive evaluation including history, physical exam, and appropriate diagnostic studies. There is a long list of pathological diseases that present as chronic pelvic pain (Table 2) that are important to consider. The etiologies of chronic pelvic pain may involve skeletal, joint, myofascial, or nerve pathology that may only be identified by thorough physical exam and directed diagnostic studies.

Without evidence of pathology, healthcare providers may contribute the complaints to be "in the head" and that may lead the patient to distrust the provider and may result in noncompliance and "doctor shopping." For both provider and patient, it can be frustrating to deal with pain that does not appear to be associated with organic pathology. While depression and other psychological disorders may be concomitantly present with chronic pelvic pain, care must be taken not to dismiss that true pathology may be present and to thoroughly investigate the complaints. It is important for the healthcare provider to acknowledge that chronic pain can lead to depression and other psychosocial problems.

5 Evaluation and Management

The initial visit for **chronic** pelvic pain should include:

1. Thorough history and physical exam that is similar to the history and physical exam as discussed above for acute pelvic pain with emphases as noted below
2. Establishment of rapport between patient and physician
3. Discussion of patient's and physician's current and future expectations

While the history and physical exam are very similar to that seen when evaluating for acute pelvic pain [see above], the chronicity of the problem changes the emphasis of concern.

Table 2. Pathological diseases associated with chronic pelvic pain in women. See Table 1 for problems usually associated with acute pelvic pain in women but may present as chronic pain

Gynecologic	Adhesions from infection or prior surgery, peritoneal cysts	Urologic	Bladder neoplasm
	Myofascial pelvic pain syndrome: contracted bands of skeletal muscles [with trigger points in the pelvic floor]		Interstitial cystitis, chronic cystitis, radiation cystitis, chronic urethritis, urethral problem
	Adnexal neoplasm or cyst		Kidney stone
	Chronic ectopic pregnancy		Detrusor dysynergia
	Pelvic infection: chlamydia, tuberculosis, subacute	GI	GI cancer
	Endometriosis		Chronic constipation, colitis, inflammatory bowel diseases, IBS
	Residual ovary syndrome		Chronic intermittent bowel obstruction
	Pelvic congestion syndrome		Diverticulitis
	Leiomyomata [degeneration] or adenomyosis	Musculoskeletal	Hernia
	Genital prolapse, levator ani spasm, piriformis syndrome, rectus muscle strain		Degenerative joint disease
Other	Nerve entrapment [old scar]		Degenerative disk disease, low back pain, poor posture
	Abdominal migraine		Myofascial pain (muscular strain, fascial inflammation), fibromyalgia, familial Mediterranean fever
	Skin: shingles, infection		Osteitis pubis

5.1 Important Elements of the History When Evaluating Chronic Pelvic Pain

- Identifying the impact that the chronic pain has had on lifestyle.
- Locations of pain [drawing picture is helpful], how "bad" it hurts, characteristics of the pain.
- Changes in pain on standing, walking, bending, sexual intercourse, menses.
  - Myofascial pain symptoms [from inflammation of soft tissues/muscles/tendons, ligaments] generally are exacerbated by movement.
- Prior injuries, medical and surgical history.
- Change of symptoms over time.
- Elicit the patient's usual bowel habits, characteristics of stool, change after bowel movement, straining, blood in stool, and constipation.
- Describe patient's normal "urinary tract function," urgency, frequency of urination, changes in symptoms with and after urination, and blood in urine.
- Weight changes, abdominal distention, hernia "bulge."
- Pain and other medications used.
- Prior workup. Laboratory and imaging study results.
- Prior interventions and success or failure of the intervention.
- Current medical problems, current psychological and psychosocial problems.

5.2 Important Elements of the Physical Exam When Evaluating Chronic Pelvic Pain

- The examination begins as the patient enters the exam room or gets onto the exam table, noticing posture, gait, limping, guarding, slow movement, forward bending, or grimacing.
- A standing exam is particularly useful when evaluating for a hernia. Checking for pain

while standing on one leg, flexion of leg to 90°, and bending down.
  - Checking for an incisional, femoral, or inguinal hernia is done by palpation with and without Valsalva.
  - Checking for pelvic floor relaxation and defect is done by placing the index finger into the vagina [with other finger in rectum] with patient bearing down.
- Sitting exam: asymmetrical or sitting forward on the chair may point to levator muscle or pelvic floor problems.
  - Examination of spine and trigger points [myofascial pain may result from repetitive motions, muscle injury, or lack of activity].
- Supine examination of abdomen.
  - Note distension, rigidness, ascites, skin changes, and previous surgical incisions and auscultation for bowel sounds.
    - Manipulate scars checking for tenderness, puckering, or fixation.
  - Examine for ease at lowering both legs, leg flexion, knee to chest, leg raising [may indicate disk disease or herniated disk].
  - Obturator sign: rotating leg with bent knee outward and inward [pain may mean internal obturator [inner upper leg] or fascial shortening, spasm consistent with myofascial pain syndrome].
  - Psoas sign: provider puts pressure on the right leg above the knee while the patient attempts to move her right hip against the pressure; greater psoas muscle attaches to top of the femur and to pelvis [right-sided positive psoas sign may be positive with appendicitis].
  - Digit palpation for trigger points in the inguinal area and then moving to area of pain eventually checking the entire abdomen, noting severity of pain with various pressures.
    - Palpation around pubic symphysis for tenderness may represent rectus muscle inflammation, injury, and osteomyelitis.
    - Rebound pain is elicited by pushing in on the abdomen and quickly releasing the pressure.
    - Palpation also noting presence of masses:
- Lithotomy examination
  - Visual inspection of external genitalia may reveal ulcerations, fistulas, and fissures that may be associated with inflammatory bowel disease.
    - Other lesions of concern include redness, discharge, excoriations, abscess, condylomata, or pigment changes.
      - Papillary lesions and areas of tenderness with pigment changes may need biopsy or colposcopic evaluation.
  - Speculum examination of the vagina
    - With and without Valsalva evaluation of cystocele, rectocele, enterocele, and uterine prolapse.
    - Palpation of levator muscles [lie adjacent to the lateral vaginal wall just above the hymenal ring] for tenderness.
    - Evaluation of the vaginal mucosa includes: redness, tenderness, discharge, lesions, atrophy, and bleeding.
  - Bimanual exam
    - Anterior vaginal urethral and trigonal areas are palpated to elicit pain response [urethral tenderness is consistent with urethritis].
    - Deep palpation of paracervical, cervical, and vaginal fornices looking for pain or mass
      - Note presence of cervical motion tenderness.
      - Trigger points in the pelvic floor muscles signal the presence of myofascial pelvic pain syndrome [discrete painful nodules].
    - Uterine size, consistency, shape, tenderness, and mobility [a uterus fixed in the cul-de-sac may be endometriosis, adhesions, infection, or cancer]
      - Nodularity of the uterosacral ligaments or sidewall [endometriosis]
    - Adnexal area is palpated for more than normal tenderness, size of adnexa, and mobility.
    - Rectal exam is done for masses, hard feces, and tenderness.

Table 3. Adjunctive diagnostic testing for acute and chronic pelvic pain

Imaging studies	Pelvic and or abdominal ultrasound, MRI, CT	Colporectocytourethrography [Dynamic U-G testing: cystourethrography, cystoproctography]
	Plain film radiology, barium enema	Hysterosalpingogram, sonohysterogram
Lab studies	CBC with differential	CA-125
	Urinalysis, urine culture	STD testing
	FSH for menopausal status	
Stool testing	Stool cultures, testing for ova and parasites	Blood in stool testing, stool DNA testing
Other	Urodynamic testing	GI function testing
	Nerve conduction and EMG studies	Cystourethroscopy
	Laparoscopy	Hysteroscopy
	Colonoscopy, sigmoidoscopy	

Management of chronic pain may be similar in part to the management of acute pelvic pain [see above]. Table 3 lists adjunctive testing for both chronic and acute pain evaluation. Additional issues and emphasis for chronic pelvic pain are discussed below:

- It is reasonable to do STD testing in women with chronic pelvic pain, particularly those with dyspareunia and urethral or cervical discharge. Urine urinalysis and culture are performed in women with urgency, bladder tenderness, and frequency. Hematuria may indicate irritable bladder, interstitial cystitis, kidney stone, cystitis, or bladder cancer.
- A GI consult or referral for colonoscopy may be indicated with positive GI findings on history or exam.
- The presence of dyspareunia, chronic pelvic pain, and dysmenorrhea are consistent with endometriosis. Laparoscopy can confirm diagnosis and allow destruction of endometrial lesion and adhesions. Treatment options for endometriosis or other uterine-related pain [dysmenorrhea, adenomyosis, and fibroids] include the levonorgestrel intrauterine device (IUD), oral contraceptive pills (OCPs), depot medroxyprogesterone acetate, and gonadotropin-releasing hormone (GnRH) agonist therapy plus add-back. NSAIDs can be used for dysmenorrhea.
- Exclusion of gastrointestinal, urinary, musculoskeletal, and psychological conditions is critical as these problems can mimic symptoms of endometriosis (the Practice Committee of the ASRM 2014).
- The optimal surgical techniques for relieving pelvic pain associated with endometriosis are not established. Long-term medical risks associated with bilateral salpingo-oophorectomy (BSO) make this option a last resort in women with debilitating symptoms (the Practice Committee of the ARSM 2014).
- There is no evidence of benefit for the use of ovulation suppression in infertile women with endometriosis who want fertility (Brown et al. 2007).
- The presence of bladder discomfort, pressure or pain, relief with voiding, urgency, and/or nocturia coupled with tenderness at bladder base and urethra indicates a diagnosis of interstitial cystitis. A voiding and intake log may better document frequency and nocturia. Ruling out a bladder infection is important. Treatment options include physical therapy, bladder hydrodistention [DMSO], amitriptyline, pentosan polysulfate sodium, antihistamines, cystoscopy, and possibly cimetidine, sildenafil, or intradetrusor botulinum toxin. Patients should be referred to a specialist when they have hematuria, bladder voiding issues, prior pelvic surgery, or radiation.
- Pelvic ultrasound, MRI, and CT are used to confirm the diagnosis of uterine fibroids, adnexal masses, and other pelvic masses. Surgical intervention may be necessary.

Musculoskeletal disorders associated with autoimmune diseases are generally referred to primary care or rheumatology. Management of adnexal and ovarian cysts and masses is needed.

- Identification of "trigger points" [painful nodules in muscles of the pelvic floor] is consistent with myofascial pelvic pain syndrome [MPPS] (Spitznagle and Robinson 2014; Wytrazek et al. 2015). The pain is thought to be due to shortening, tightening, and/or irritation caused by repetitive movements, injury, or disuse. These trigger points may cause referred pain to the bowel, bladder, thighs, lower abdomen, or buttocks and may cause sexual problems (Pendergast and Weiss 2003; FitzGerald and Kotarinos 2003). The cause of the condition is unclear; however, the etiology is believed to be related to trauma to the various activities that involve the pelvic muscles including movement, support of pelvic and abdominal structures, and control of bladder and bowel function. MPPS can be caused or exacerbated by infection or estrogen deficiency-related atrophy. The muscles involved include levator ani, obturator internus, bulbospongiosus, ischiocavernosus, sphincter ani, transversus perineum, piriformis, and pubococcygeus. Women with this condition often complain of pain in the vagina, vulva, pelvis, bladder, or rectal area and may present with gait, range of motion, and walking problems. Referral to a physical therapist and counseling regarding stretching exercises, heat or ice, and oral pain medication are indicated. Other treatment options include "stretch and spray" technique [spraying area with coolant and then stretching] and injection of trigger points.
- The American College of Obstetricians and Gynecologists (ACOG) suggests physical therapy, acupuncture, acupressure, and nerve stimulation therapies for treating pain caused by dysmenorrhea. They also recommend physical therapy that relieves "trigger points" for muscular pain and physical therapy teaching "relaxation" techniques, relaxation exercises, and biofeedback (American College of Obstetricians and Gynecologists 2014).

6 Cyclic Recurrent Pelvic Pain

Recurrent pelvic pain includes "Mittelschmerz," dysmenorrhea, adenomyosis, and pelvic congestion syndrome that may vary with the menstrual cycle. Premenstrual syndrome is known to cyclically affect a variety of symptoms (Rapkin and Karnes 1988). Additionally there are several diseases, such as irritable bowel symptoms, that may vary in severity throughout the menstrual cycle (Rapkin and Mayer 1993).

Treatment for cyclic recurrent pelvic pain includes the levonorgestrel intrauterine device (IUD) ["Mirena" IUD], combination oral contraceptive pills, NSAIDS, depot medroxyprogesterone acetate, progestin-only pills, and gonadotropin-releasing hormone (GnRH) agonist therapy with add-back. This treatment is also used for pelvic congestion syndrome that can be diagnosed with MRI or laparoscopy. Laparoscopic uterine nerve ablation (LUNA) does not appear to offer any benefit over conservative surgery for endometriosis alone (the Practice Committee of the American Society of Reproductive Medicine [ASRM] 2014). The oral progesterone receptor blocker ulipristal acetate [used in the USA for emergency contraception] is reported to be as effective as once-a-month leuprolide acetate in decreasing uterine bleeding in women with uterine fibroids and significantly less likely to cause hot flashes (Donnez et al. 2012).

7 Conclusion

Pelvic pain in women can be caused by a variety of organ systems including gynecological, gastrointestinal, urological, musculoskeletal, and vascular. It may represent a life-threatening condition, have a chronic negative impact on quality of life and lifestyle, or necessitate nonemergency surgical intervention. A careful history and physical

exam followed by appropriate laboratory and diagnostic studies enable healthcare providers to continually narrow the list of potential diagnoses. Quickly ruling out critical or life-threating conditions is particularly important in women presenting with acute pelvic pain.

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Treatment of Amenorrhea

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Contents

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Abstract

There are many different causes for amenorrhea. Having a systematic way to think about and work up the causes will help you diagnose the etiology. Causes of amenorrhea can be broken down into structural and endocrine categories. Structural causes are either due to congenital abnormalities such as those seen with primary amenorrhea or acquired, including cervical stenosis or Asherman syndrome. Endocrine causes are associated with dysfunction of the ovary, pituitary, or hypothalamus. Dysfunction of the ovary can be either due to chronic anovulation from polycystic ovary syndrome, obesity, thyroid dysfunction, or hyperprolactinemia. The other major cause of ovarian dysfunction is due to primary ovarian insufficiency/diminished ovarian reserve. Pituitary disorders can be endocrine or structural, with aberrant production of hormones or mass effect interrupting the normal hypothalamic-pituitary-ovarian (HPO) axis. Hypothalamic etiologies stem from congenital deficiencies such as Kallmann syndrome or dysfunction/failure from weight loss, heavy exercise, or emotional/psychological stress. The first visit with a patient should include a thorough history and physical exam. Initial labs such as urine HCG, TSH, prolactin, FSH, and estradiol are important for screening for the most common etiologies of amenorrhea. In addition, these also are the first step in assessing the status of the HPO axis in order to discover the underlying reason for amenorrhea.

Keywords

Amenorrhea • Anovulation • Primary ovarian insufficiency • PCOS • Müllerian anomaly

1 Introduction

Amenorrhea, the absence of menses, is normal prior to menarche, after menopause, and during pregnancy and lactation (ASRM 2004). In the USA, the average age for the onset of menarche is approximately 12.3 years old, while the average age of menopause is 51.4 years old (Anderson et al. 2005; Kato et al. 1998). The absence of menses prior to or after these parameters must be investigated. Amenorrhea can be physiologic or pathologic, and its etiologies are best classified into endocrine or structural categories. The prevalence of amenorrhea is around 3–4% (Pettersson et al. 1973).

2 Primary Amenorrhea

Primary amenorrhea is defined by the following:

1. Absence of menses by age 15 regardless of the presence of normal secondary sexual characteristics (or up to 5 years after breast development if it occurs prior to age 10)

Table 1 Etiologies of primary amenorrhea

Chromosomal abnormalities	43%
Müllerian agenesis	15%
Constitutional delay	14%
Polycystic ovary syndrome	7%
GnRH deficiency	5%
Transverse vaginal septum	3%
Anorexia, weight loss, stress	2%
Pituitary disease	2%
Others: imperforate hymen, androgen insensitivity syndrome, pituitary tumor, congenital adrenal hyperplasia, hypothyroidism, CNS defect, Cushing's disease, craniopharyngioma	9% (~1% each)

2. Failure to start breast development and menses by 13 years old (Table 1)

3 Secondary Amenorrhea

Secondary amenorrhea is defined by:

The absence of irregular menses for 6 month or the length of time equivalent to three prior menstrual cycles (i.e., 84 days for a 28-day cycle) (Table 2)

An evaluation and workup may be warranted even if the above criteria are not met, such as evidence of not meeting pubertal milestones or having stigmata of disorders of sexual development.

The etiologies for amenorrhea can be broken down into different categories, which may guide provider workup. The World Health Organization (WHO) categorizes etiologies of amenorrhea into different groups (Table 3).

There are overlapping causes for primary and secondary amenorrhea; thus the general causes are broken down into the following:

1. Anatomic:
   (a) Genital outflow tract disorders
   (b) Congenital anomalies of the uterus
2. Endocrine: ovarian disorders
3. Endocrine: anterior pituitary disorders
4. Central nervous system disorders

4 History

The history taking should be thorough and tailored to the patient's presentation. Inquiring about pubertal milestones and a family history of delayed puberty is indicated in a girl or woman who presents with primary amenorrhea, has stigmata for Turner disease, or has not fully developed secondary sexual characteristics.

Clinicians should take an accurate account of patient's personal and/or childhood health as well as current physical, emotional, or psychological stressors. One should assess for lifestyle habits such as diet, exercise, and changes in weight. It is important to elicit symptoms of galactorrhea, virilization (balding, changes in dark hair growth,

Table 2 Etiologies of secondary amenorrhea

Ovarian dysfunction	40%
PCOS	30%
Primary ovarian insufficiency	10%
Hypothalamic amenorrhea	35%
Pituitary dysfunction	17%
Uterine adhesions	7%
Others: congenital adrenal hyperplasia, ovarian or adrenal tumor, hypothyroidism	1%

Table 3 WHO classification for amenorrhea

Characteristic	Group I	Group II	Group III=
Estrogen	Low	Normal	Low
FSH	Low/normal	Normal	High
Prolactin	Normal	Normal	
Hypothalamus/ pituitary	No pathology		
Example	Hypogonadotropic hypogonadism	Polycystic ovary syndrome (PCOS)	Primary ovarian insufficiency (POI)

acne, or deepening of voice), or changes associated with thyroid dysfunction such as heat or cold intolerance, changes in bowel movements, and energy level. It is also necessary to inquire about any symptoms of brain mass such as headaches or visual changes. Lastly, but still importantly, a thorough medication list should be recorded.

5 Physical Exam

Physical exam should include vital signs and body mass index. Providers should evaluate and document normal breast development, signs of virilization (hirsutism, acne), skin examination (evaluating for striae, pigmentation, vitiligo), and presence of stigmata of Turner syndrome (low hairline, webbed neck, shield chest, widely spaced nipple short stature).

6 Genitourinary Exam

The inguinal region should be palpated for any masses, and a careful genital exam should be performed, taking note of clitoral size; pubic hair tanner stage; the hymen (presence or absence); depth of the vagina; presence of the cervix, uterus, and ovaries; and any abnormalities. If a genital exam is not feasible (particularly in younger girls), then an abdominal ultrasound may be ordered to assess for the presence or absence of the uterus.

6.1 Normal Pelvic Anatomy

A patent vagina, visible cervix, and palpable uterus exclude congenital outflow abnormalities. This, however, does not exclude cervical stenosis or uterine synechiae (scarring). The latter two may be evaluated with sonohysterography or a hysteroscopy if indicated by the patient's history.

6.2 Abnormal Pelvic Anatomy

The embryology of the female genital tract involves:

1. Medial migration and midline fusion of the paramesonephric and müllerian ducts, which ultimately form the uterus, cervix, and upper vagina.
2. Urogenital sinus invaginates to form the lower vagina and introitus.

Abnormalities during formation of these structures can lead to imperforate hymen, transverse vaginal septum, and cervical atresia. Pelvic ultrasound can be ordered to better evaluate the genital tract and presence or absence of any organs.

7 Ovarian Function

If history and physical exam do not arouse suspicion for a genital tract abnormality, a hormonal workup must be initiated. The most common etiology for amenorrhea is ovarian dysfunction. Disorders include chronic anovulation or oligo-ovulation secondary to thyroid dysfunction, hyperprolactinemia, polycystic ovary syndrome, obesity, or primary ovarian insufficiency.

8 Laboratory Workup

The initial workup for someone with amenorrhea includes a urine human chorionic gonadotropin (hCG) to exclude pregnancy.

> Pregnancy is the most common etiology for secondary amenorrhea. Other laboratories to include in the workup are thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), and estradiol (E2). The TSH and PRL are to evaluate for thyroid dysfunction and hyperprolactinemia.

Table 4 Expected gonadotropin and estradiol levels in different ovarian disorders

Ovarian functional status	Serum FSH	Serum LH	Serum estradiol
Normal:	5–20 IU/L	5–20 IU/L	>40 pg/mL
Normal			
Chronic anovulation			
Hypogonadotropic hypogonadism:	<5 IU/L	< 5 IU/L	<40 pg/mL
Prepuberty			
Hypothalamic dysfunction			
Pituitary dysfunction			
Hypergonadotropic hypogonadism:	>20 IU/L	> 40 IU/L	<40 pg/mL
Primary ovarian insufficiency			
Diminished ovarian reserve			
Surgical menopause			

The FSH and estradiol are to evaluate the state of the hypothalamic-pituitary-ovary axis. A cell blood count (CBC), chemistry panel, and a basic urinalysis can be ordered to exclude system disease.

8.1 Estrogen Measurement

Normal levels of estradiol are typically seen with anovulation. Low estradiol levels are seen in women with ovarian failure, hypothalamic dysfunction, or pituitary disorders. However, since estradiol levels normally fluctuate, a single normal or low level may not be sufficient to make a diagnosis. In addition, patients with primary ovarian insufficiency, pituitary dysfunction, or hypothalamic amenorrhea may regain intermittent ovarian function and sporadically ovulate and produce estradiol.

8.2 Gonadotropin Measurement

Routine evaluation of serum FSH in conjunction with estradiol levels in amenorrhea can be helpful in assessing ovarian dysfunction. High levels of FSH are typically associated with either ovarian insufficiency or follicular depletion (i.e., diminished ovarian reserve). Low levels of estradiol production prevent negative feedback on the hypothalamus and thus increase release of FSH from the pituitary to stimulate estradiol production. Exceptions to this are highly unlikely, but include mutations in the LH or FSH receptor, ectopic production of FSH by a tumor, or an enzyme deficiency leading to low or undetectable estradiol levels (aromatase or 17-alpha-hydroxylase). Given that LH production is similar to FSH, levels are not typically as helpful in assessing amenorrhea.

A low or normal FSH can signify a few different things. FSH can be low in the setting of functional ovarian follicles, anovulation, pituitary disease, or hypothalamic dysfunction. Above is a table with reference ranges and possible diagnoses (Table 4).

9 Endometrial Stripe on Ultrasound

Transvaginal ultrasound can be used to assess endometrial thickness, which reflects endometrial proliferation and may provide information regarding estrogen levels. A woman that is hypoestrogenic is more likely to have a thin endometrial stripe. In any woman with a prolonged history of anovulation, endometrial biopsy to exclude hyperplasia should be considered.

10 Progesterone Challenge

In addition to the initial workup with TSH and prolactin, a progesterone challenge can be performed. If a woman has sufficient circulating estrogen to build up her endometrium, the progestin challenge should induce menses. However, it is important to note that the sensitivity and specificity for assessing estrogen status with this test are low (Nelson 2009).

10.1 Positive Test

Positive tests are defined by bleeding 2–7 days after completing the progestin regimen. Of note, if a patient has a delay in her bleeding, approximately 14 days after the progesterone challenge, then this medication has either been an inadequate dose of progestin, there is an outflow obstruction, or less likely, the medication has triggered ovulation.

A positive test indicates normal circulating estrogen and anovulation (and confirms a patent outflow tract). Further evaluation is not necessary as long as the patient has a normal TSH and prolactin and the absence of galactorrhea.

In those with prolonged periods of anovulation, endometrial biopsy should be performed to exclude endometrial hyperplasia. Patients diagnosed with anovulation are recommended to have regular cyclic exposure to progestin therapy (or combined estrogen-progestin combination) to prevent constant estrogenic stimulation of the endometrium, which can lead to hyperplasia and malignancy over time.

Regimens for medical management for anovulatory patients include cyclic medroxyprogesterone 10–40 mg po daily 10–14 days every month. A combined estrogen-progestin contraceptive such as oral contraceptive pills, vaginal ring, or transdermal patch is also an option. Levonorgestrel IUD is an option for patients desiring a long-term contraception, requiring minimal effort after insertion. Etonogestrel implant and Depo-Provera injection are also additional options for contraception and progestin exposure.

10.2 Negative Test

If a patient only has a small amount of spotting after the progestin challenge, there is endogenous estrogen production, but this may indicate marginal levels and warrants further monitoring and possible workup.

Complete absence of progestin withdrawal bleed indicates two possible disorders – Asherman syndrome or absence of estrogenization of the endometrium to induce proliferation.

Further workup is based on history – evaluation of the endometrial cavity for suspected Asherman syndrome and gonadotropin and karyotype workup for possible POI.

11 Normal Gonadotropin Levels

11.1 Ovarian Disorders Related to Chronic Anovulation

Normal serum FSH and estradiol are suggestive of chronic anovulation. The most common etiologies for this include polycystic ovary syndrome (PCOS), obesity, excessive exercise, ovarian aging, thyroid dysfunction, and hyperprolactinemia. Typically, anovulation secondary to excessive stress, whether it is emotional, physical, or nutritional, is a diagnosis of exclusion. However, a careful history and physical exam may support this diagnosis. Treatment of the underlying etiology is important. Addressing

dietary, lifestyle, and behavioral issues may eventually lead to return of menstrual cycles.

11.2 Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome is the most common diagnosis for chronic anovulation. Based on recommendations from the Androgen Excess PCOS Society (Azziz et al. 2006), it is defined as:

1. Excess androgen activity
2. Chronic oligo- or anovulation and polycystic ovaries
3. Exclusion of other etiologies for excess androgen status

There are other definitions for PCOS, including the 2003 Rotterdam Criteria and the 1991 NIH criteria. All definitions are in agreement that the constellation of anovulation and androgen excess are the basis for the diagnosis of PCOS. Workup for suspected PCOS includes the typical amenorrhea workup (TSH, prolactin, HCG), along with serum testosterone, DHEAS, FSH, and LH to exclude other disorders. Given the increased risk for metabolic dysfunction, screening for dyslipidemia and glucose intolerance is also recommended with fasting lipid panel, fasting glucose, and 2 hour oral glucose tolerance test.

11.2.1 Endometrial Sampling

If one is concerned for chronic anovulation in the setting of unopposed estrogen, endometrial sampling is indicated to exclude endometrial hyperplasia or malignancy.

Patients with PCOS, obesity, and long periods of anovulation are at the highest risk for disease (Aune et al. 2015). There are no studies specifically examining endometrial thickness on pelvic ultrasound and associations with pathology in the premenopausal woman; thus clinical judgment is important in deciding who should have endometrial sampling.

In addition, periodic (cyclic) exposure to progesterone/progestin is important to prevent hyperplasia and malignancy.

In patients desiring pregnancy prevention options include, cyclic combined estrogen-progestin or progestin-only contraception options are OCPs, transdermal patch, etonogestrel/ethinyl estradiol vaginal ring, levonorgestrel IUD, etonogestrel implant, or medroxyprogesterone injection. In those not desiring pregnancy, cyclic progestin either monthly or every other month can be given.

11.3 Thyroid Dysfunction

A small proportion of patients with amenorrhea will have thyroid dysfunction without any other clinical symptoms. To assess for thyroid function, a TSH and free T4 are drawn together or free T4 can be drawn in the setting of an abnormal TSH. Primary hypothyroidism is associated with an elevated TSH and low free T4, and primary hyperthyroidism is associated with a low TSH and elevated free T4. An elevated TSH and normal free T4 define subclinical hypothyroidism. In the setting of infertility or menstrual dysfunction, it is recommended to treat the thyroid disorders, even in subclinical hypothyroidism (SCH) as many patients are diagnosed in their progression toward frank hypothyroidism.

11.4 Treatment

If someone is planning pregnancy, normalization of TSH levels to 0.1–2.5 mIU/L prior to pregnancy and during the first trimester and to 0.2–3.0 mIU/L in the second and third trimesters is indicated to minimize

the potential neurological effects of hypothyroidism on the developing embryo and fetus (ACOG 2015).

Typical initial doses for the treatment of hypothyroidism are 1–2 mcg/kg orally daily (or 100 mcg daily for most) followed by rechecking TSH levels in 1 month and adjusting base on response (Garber et al. 2012). Levels may be checked after 2 weeks if the disease is severe. For women with SCH attempting conception, the American Society for Reproductive Medicine states there is good evidence for treating women with TSH >4 mIU/L to improve pregnancy and miscarriage rates and decrease risk of adverse neurodevelopmental outcomes. They also state there is insufficient evidence that treatment of SCH with a TSH between 2.5 and 5 mIU/L is associated with improved outcomes (ASRM 2015).

If there is a normal free T4 and a low TSH, serum triiodothyronine (T3) can be checked as an elevated value indicates hyperthyroidism, which must also be corrected. Methimazole 10–40 mg orally daily divided into two or three doses and propylthiouracil 50–150 mg daily divided into three times per day are both reasonable regimens (Garber et al. 2012). We recommend that an endocrinologist manage these medications.

Another point of consideration is that hypothyroidism leads to elevated levels of thyroid-releasing hormone (TRH), which can stimulate prolactin production, causing hyperprolactinemia and possibly symptoms of galactorrhea. Elevated prolactin levels caused by hypothyroidism are typically less than 100 ng/mL. Also of note is that a longer duration of hypothyroidism can lead to decreasing levels of dopamine (inhibitory for prolactin production), and this can lead to unopposed stimulation of prolactin production by TRH. Treatment of hypothyroidism may correct hyperprolactinemia, with a slight lag in resolution of galactorrhea, over the course of months (Poretsky et al. 1986).

11.5 Hyperprolactinemia

Prolactin measurement is indicated in any amenorrhea workup. High levels may affect pubertal development; thus checking levels is even indicated in cases of primary amenorrhea. High levels of prolactin are thought to affect GnRH pulsatility, leading to decreasing levels of gonadotropins and hypogonadism. Mild elevations in prolactin levels (20–50 ng/mL) may be seen with stress, intercourse, and sleep, thus requiring repeat lab testing to establish a diagnosis of hyperprolactinemia. A fasting prolactin level can be drawn for accuracy, and if elevated (using the assay's reference range), imaging of the sella is recommended. MRI of the pituitary is recommended to exclude a mass, such as a prolactinoma or other tumor causing mass effect on the pituitary stalk, disrupting dopamine release. Other etiologies for hyperprolactinemia include hypothyroidism and medication. Medications that inhibit dopamine action or decrease levels, leading to hyperprolactinemia include (Molitch 2005):

- First-generation antipsychotics (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thiothixene, trifluoperazine)
- Second-generation antipsychotics (paliperidone, risperidone, asenapine, ziprasidone, olanzapine, and less commonly clozapine, iloperidone, lurasidone, quetiapine)
- Tricyclic antidepressants (clomipramine, amitriptyline, desipramine)
- Selective serum reuptake inhibitor antidepressants (low risk – citalopram, fluoxetine, paroxetine, sertraline, fluvoxamine)
- Antiemetics (metoclopramide, prochlorperazine, domperidone) antihypertensive (methyldopa, verapamil)
- Opioid analgesics (methadone, morphine, etc.)

Other causes of prolactin elevations are physiologic: pregnancy, nipple stimulation, exercise, breast exams, and stress. Pathologic causes include lactotroph adenomas, hypothalamic or pituitary masses or disease affecting dopamine

and prolactin, germline loss-of-function mutations of the prolactin receptor gene (*PRLR*), idiopathic elevated estrogen, and chronic renal insufficiency. Rare other causes of prolactin elevations include ectopic pituitary tissue found in the pharynx, bronchogenic carcinoma, renal cell carcinoma, gonadoblastoma, or even dermoid cyst/teratoma in the ovary.

11.6 Treatment

Stopping suspect medications and/or treating the underlying disease (i.e., hypothyroidism) should be done as indicated. Treatment for hyperprolactinemia is indicated in the following situations:

- Macroadenoma causing neurologic symptoms or abutting/invading the optic chiasm and cavernous and sphenoid sinuses
- Symptomatic hyperprolactinemia (galactorrhea) and hypoestrogenism (amenorrhea)
- Patients interested in conception

Treatment for symptomatic hyperprolactinemia is primarily done with dopamine agonists (Melmed et al. 2011). First-line treatment is cabergoline (0.25–1 mg by mouth twice weekly, with dose adjustments based on prolactin level). Cabergoline tends to have the best side effect profile. There is a slight increase in risk of valvular heart disease, but is uncommon in the doses used to treat hyperprolactinemia. Bromocriptine is second line (2.5–15 mg by mouth daily), adjusting for prolactin levels. Other medications not available in the USA include pergolide and quinagolide. The goals are to decrease the size of a microadenoma, improve symptoms related to hyperprolactinemia, and normalize menstrual function. If patients have hyperprolactinemia from a microadenoma and do not want to conceive or take dopamine agonists, combined oral hormonal contraception can be used. Further treatment for hyperprolactinemia is discussed below.

Anatomical etiologies for amenorrhea can be associated with normal gonadotropins and are discussed in further detail below.

12 Elevated Gonadotropin Levels

12.1 Primary Ovarian Insufficiency

The presence of elevated gonadotropins is concerning for primary ovarian insufficiency (POI). This diagnosis is defined by oligomenorrhea or amenorrhea × 3 cycle lengths, elevated FSH >30–40 IU/L, and symptoms concerning for POI prior to age 40 (hot flashes, irritability, vaginal dryness). When suspicious for POI, a workup for chromosomal, genetic, and autoimmune etiologies is indicated.

12.2 Initial Workup

The initial basic workup for POI includes documenting elevated FSH values (two), TSH, and prolactin. When these confirm the diagnosis, a karyotype is indicated. Once POI is established either with normal or abnormal karyotype, hormone replacement therapy and monitoring of bone health via DEXA scan are recommended at least until age 50.

12.3 Genetic Abnormalities

Karyotype is the first step indicated in the workup for POI, especially if it occurs <30 years old. A karyotype will reveal deletions, mosaicism, and translocations. It is important to diagnose conditions such as Turner syndrome or mosaic, which have implications on cardiovascular, renal, and bone health. Further description regarding disorders of gonadal dysgenesis is discussed below.

Fragile X premutation and autoimmune etiologies are the next most common reasons for POI.

Workup includes testing for *FMR1* premutation carrier status for fragile X and testing of anti-21-hydroxylase antibodies for autoimmune disease. More detail and workup of other etiologies for POI are listed below.

13 Low Gonadotropins

13.1 Hypothalamic Amenorrhea

Amenorrhea accompanied by low estradiol and low to normal gonadotropins is concerning for hypothalamic failure. MRI with contrast study of the sella is generally recommended in patients with hypothalamic failure. Below we detail clinical investigation, different etiologies, workup, and treatments for hypothalamic amenorrhea. Hypothalamic dysfunction is generally seen with low follicular level estradiol and low to normal gonadotropins accompanied by irregular menses or oligomenorrhea.

14 Specific Causes of Amenorrhea

14.1 Disorders of Amenorrhea by Compartment

I. Anatomical:
   (a) Asherman syndrome
   (b) Genital outflow tract disorders
   (c) Congenital anomalies of the uterus
II. Endocrine: ovarian disorder
   (a) Abnormal chromosomes
   (b) Normal chromosomes
III. Endocrine: anterior pituitary disorder
   (a) Prolactin tumors
IV. Central nervous system disorders
   (a) Anovulation
   (b) Weight loss/anorexia
   (c) Hypothalamic suppression
   (d) Hypothyroidism

Table 5 A list of outflow tract abnormalities causing amenorrhea

Acquired	Asherman syndrome
	Cervical stenosis
Congenital	Complete androgen insensitivity
	Imperforate hymen
	Transverse vaginal septum
	Müllerian agenesis

15 Anatomic Causes of Amenorrhea (Table 5)

15.1 Disorders of the Outflow Tract and Uterus

Physical exam and pelvic imaging can help characterize outflow tract disorders.

16 Asherman Syndrome

Asherman syndrome is defined as uterine synechiae and/or scarring, due to destruction of the functional lining of the uterus after uterine instrumentation. Clinically, it can present with amenorrhea, hypomenorrhea, dysmenorrhea, miscarriage, and/or infertility. Uterine synechiae typically form in the setting of infection and uterine scarring or postpartum curettage in the setting of hemorrhage or septic abortion (Berman 2008). Uterine artery embolization can also lead to ischemia of the endometrium and potentially Asherman syndrome (Davies et al. 2002). Uterine tuberculosis (TB) and uterine schistosomiasis can also cause endometrial damage, which can present similarly to Asherman syndrome. These are rare in developed countries but can be diagnosed with endometrial biopsy (TB) or testing for parasite eggs in urine, feces, or endometrium.

Initial workup for Asherman syndrome is done with sonohysterography. Diagnosis via hysteroscopy is the gold standard, as you can treat the adhesions at the same time. Hysteroscopic lysis of adhesions or removal of synechiae is recommended if this is identified, as consequences of Asherman syndrome include partial obstruction of functional endometrium leading to dysmenorrhea and outflow obstruction or

infertility. For operative hysteroscopy, lysis of synechiae can be performed with scissors, cautery, myosure, or laser; however, scissors are associated with less postoperative adhesions (Yu et al. 2008). If there are severe adhesions obliterating the uterine cavity, concurrent laparoscopy or abdominal ultrasound guidance can be used to assist help in avoiding uterine perforation while completing the extensive resection. To prevent scar tissue reformation, a pediatric Foley catheter can be inserted, filled with 3 mL of fluid, sutured occlusion of outflow, and removed after 10 days. Alternatives can be placement of an intrauterine device, kept in place for 3 months, or insertion of hyaluronic acid, which is an adhesion barrier. Some practices routinely perform repeat hysteroscopy 10–14 days after treatment to visualize and treat any filmy adhesion reformation. If a Foley is inserted, broad-spectrum antibiotics should be given for 10 days (or for the duration of time the Foley catheter is in), such as doxycycline 100 mg orally twice daily. A comparison of Foley, IUD, and hyaluronic acid on retrospective review showed that Foley was associated with the least amount of adhesion reformation, followed by IUD and hyaluronic acid (Lin et al. 2013). Most physicians will also prescribe estrogen therapy for 4 weeks to stimulate endometrial proliferation. The regimen is 2.5 mg oral conjugated equine estrogen twice daily (or oral estradiol 4 mg twice daily), followed by progestin therapy (medroxyprogesterone acetate 10 mg po daily or norethindrone acetate 2.5 mg oral daily) during the last 10 days of estrogen therapy.

17 Cervical Stenosis

Cervical stenosis may be a result of scarring from surgery on the cervix for severe dysplasia such as a cold knife cone, laser, LEEP, or rarely cryotherapy. Presentation includes cyclic pelvic pain or light spotting instead of normal menstrual flow. Treatment of this includes manual cervical dilation and occasionally temporary balloon catheter placement for 2 weeks to help decrease recurrence.

18 Androgen Insensitivity Syndrome

Androgen insensitivity syndrome (AIS) is also known as testicular feminization and is a disorder caused by a mutation in the androgen receptor (located on the X chromosome long arm), thus leading to end-organ insensitivity to androgen. Patients with AIS have a 46,XY karyotype and testes or gonadal remnants that may be intraabdominal, in the inguinal canal, or partially descended. During embryology, the presence of gonadal tissues results in the production of antimüllerian hormone that blocks the formation of a uterus or fallopian tubes. Externally, these patients have a short, blind-ending vagina and no testicular or penile growth due to lack of androgen receptors. They will develop breasts secondary to estrogen derived from peripheral aromatase conversion of circulating testosterone to estrogen. On examination, these patients are sometimes called "super feminine" as they have scant or no pubic or axillary hair due to their androgen insensitivity, no facial hair, and often fully developed or large breasts.

> The most typical presentation in the adolescent period is complaint of primary amenorrhea (without cyclic pelvic pain due to the lack of müllerian structures)

Laboratory values will reveal elevated testosterone. Pelvic ultrasound will reveal lack of a uterus, cervix, or ovaries. Treatment for AIS includes options for vaginal reconstruction as seen for müllerian agenesis. Gonadectomy of residual gonadal tissue is recommended due to the increased risk of neoplasia, usually done after pubertal development occurs as tumors occur most commonly after puberty (Purves et al. 2008). In partial AIS, gonadectomy can be performed sooner to prevent virilization in a phenotypically appearing female.

19 Imperforate Hymen

Imperforate hymen may be caused by genetic factors, although it has not been well defined (Lim et al. 2003). The imperforate hymen can present in different ways, with the most common being cyclic pelvic or abdominal pain from buildup of menstrual blood in the adolescent period. It can also present with perineal pain or urinary retention from urethral obstruction. On physical exam, the vaginal orifice appears non-patent with a perineal bulge representing hematocolpos. An MRI should be obtained to rule out other GU tract abnormalities such as transverse vaginal septum as the treatment is different. In cases of imperforate hymen, menstrual buildup can lead to retrograde menstruation causing endometriosis as well as inflammatory changes in the pelvis.

Surgical treatment is recommended in the operating room with a goal to open the membrane and allow for tampon use and eventually sexual intercourse. The hymen is incised in a cruciate fashion at 2, 4, 8, and 10 o'clock. A vertical or U-shaped incision can be used as well. It is important to avoid making the incision too close to the vaginal mucosa as it may cause scarring, stenosis, and dyspareunia (Dominguez et al. 1997).

20 Transverse Vaginal Septum and/or Cervical Atresia

A transverse vaginal septum is caused by failure of canalization of the vaginal plate during embryogenesis. The septum is usually positioned between the upper one third and lower two third of the vagina. Symptoms of transverse vaginal septum may be similar to those of imperforate hymen – cyclic pelvic pain and/or vaginal bulge or dimple detected in the adolescent age. Younger girls can present with mucocolpos. In some cases, microperforations allow bacteria to ascend causing pyohematocolpos. On physical exam, a vaginal bulge may be present from hematocolpos, but the position is different from the imperforate hymen as the imperforate hymen is located on the introitus, not the upper vagina. Pelvic ultrasound may be helpful to evaluate the uterus and adnexa, but MRI is a better study to help distinguish a septum from cervical atresia and to measure the size of the septum that aids in surgical planning (Reinhold et al. 1997). Dilators may be used preoperatively to thin the septum to facilitate removal. Removal is done with a vertical or "Z-plasty" incision to minimize scarring (Garcia 1967). We recommend that an experienced surgeon perform this procedure.

21 Müllerian Agenesis (Mayer-Rokitansky-Küster-Hauser Syndrome: MRKH)

Müllerian agenesis is the congenital absence of a vagina and variations of uterine development that includes bilateral or unilateral uterine horns, a hemiuterus, a midline uterus with no cervix, or a complete absence. Presentation of MRKH is usually primary amenorrhea in a girl or young woman with normal secondary sex features. In 10% or less of patients, there may be functional endometrium, and patients may present with cyclic pelvic pain. MRKH is thought to have a genetic component, as there are descriptions in the literature of familial cases with variable expression.

- Galactose-1-phosphate uridyl transferase gene mutations (GALT) have a higher prevalence in women with müllerian agenesis (Fedele et al. 1990).
- MRKH is associated with skeletal abnormalities and, in particular, the Klippel-Feil syndrome (low hairline, short neck, and pain associated with cervical vertebrae fusion) as well as VACTERL (vertebral anomalies, anal atresia, cardiovascular anomalies, esophageal atresia, renal anomalies, limb anomalies) (Rall et al. 2015).

The workup for MRKH includes karyotype to rule out androgen insensitivity syndrome and male pseudohermaphroditism, pelvic ultrasound (not mandatory – but can help evaluate remnant pelvic structures), and MRI. Given the association

with renal and skeletal abnormalities, renal ultrasound and spinal x-rays should be ordered as well.

In certain candidates, there is a role for vaginal reconstruction surgery for sexual function. Different techniques exist, including the McIndoe (construction of neovagina using a skin graft), the Vecchietti operation (dissection of the vesicorectal space followed by internal stretching of the vaginal remnant), and laparoscopic modifications of the Vecchietti. Surgical candidates must be committed to using dilators post-procedure to maintain vaginal length and functionality. Fertility options include in vitro fertilization with oocyte retrieval and gestational surrogacy. More recently, uterine transplant has become a potential option, but remains experimental at this time (Jones et al. 2016).

22 Endocrine: Ovarian Disorders

22.1 Abnormal Chromosomes

22.1.1 Gonadal Dysgenesis

Gonadal genesis is the most common etiology for primary amenorrhea, making up to 30–40% of cases. It is caused by an X chromosome abnormality or defect in other genes involved in germ cell migration and/or organization. Patients have absent or incompletely formed gonads that are present as ovarian remnants. Some patients have a 46,XX karyotype, some 45,X. Turner syndrome is the most common etiology for gonadal dysgenesis.

- There is also a syndrome associated with gonadal dysgenesis and sensorineural deficit known as Perrault syndrome (Meyers et al. 1996).

22.1.2 Turner Syndrome

Turner syndrome is caused by the absence of one complete or partial copy of the X chromosome in some or all the cells. The karyotype of Turner syndrome includes monosomy (45,X), mosaicism (45,X/46,XY), partial monosomy (46X, del(Xp), or presence an isochromosome of two q arms (46, X,i(Xq)).

Approximately 10–20% of Turner patients have spontaneous puberty, and 25% have spontaneous menses (Pasquino et al. 1997; Hadnott et al. 2011). Some patients may have spontaneous pregnancy as well, but may be at increased risk for chromosomal abnormalities in the offspring and/or miscarriage. Turner can also present as abnormal pubertal development and primary amenorrhea. Physical characteristics include short stature, webbed neck, widely spaced nipples, and shield chest. If a patient has mosaicism and a Y chromosome, the gonads may contain some testicular tissue and have an elevated risk for developing cancer, including gonadoblastomas, dysgerminomas, yolk sac tumor, and choriocarcinoma. Onset of germ cell tumors is typically less than 20 years old, with a cumulative risk of 7.9% by age 25 (Schoemaker et al. 2008).

Turner syndrome has implications on cardiovascular, renal, and bone health. Some of the associated cardiac anomalies are bicuspid aortic valve, coarctation, and other malformations (Cramer et al. 2014). Referral to cardiology is warranted with this diagnosis between 12 and 15 years old (or at diagnosis), and repeat echocardiogram is recommended every 5 years for any Turner patient. If the echocardiogram is abnormal, then echo is obtained more frequently, as determined by the cardiologist. In addition, a renal ultrasound should be obtained upon diagnosis and only repeated if abnormal (every 3–5 years). Turner patients have higher rates of thyroid dysfunction, and TSH and free T4 should be ordered on diagnosis and repeated every 1–2 years. Given the increased risk for metabolic dysfunction, hypertension, renal, and liver disease, labs including CBC, fasting glucose, fasting lipid profile, and chemistry panel (including creatinine and LFTs) are recommended every 2 years (Freriks et al. 2011). Other things to screen for are celiac disease (anti-endomysial antibodies) as well as audiometry (to be followed every 10 years or more frequently if abnormal). For patients that are

diagnosed early on, growth hormone treatment may help achieve more height.

22.1.3 Hormone Replacement Therapy

Patients with Turner are at risk for effects of hypoestrogenism, thus treatment with exogenous hormones is recommended. Therapy should start between ages 12 and 15 (allowing maximization of height). Dosing is 0.25–0.5 mg micronized estradiol or equivalent, increasing every 3–6 months depending on development of secondary sex characteristics. The goal is to complete tanner stage/sexual maturation after 3 years. Progestin therapy can be added with the first episode of vaginal bleeding for 1–2 years after onset of estrogen therapy to avoid unopposed estrogen exposure. Switch over to combination oral contraceptives ensures adequate estrogen treatment. Consideration of transdermal testosterone to reverse the often very low androgen levels is less frequent but is beneficial for muscle, bone, and skin. Turner patients may have infertility and may be candidates for in vitro fertilization with oocyte donation. Gestational surrogacy should be considered, as with the comorbidities, a high-risk pregnancy with an increased risk of death needs to be considered.

22.1.4 Swyer (46 XY Gonadal Dysgenesis)

Swyer syndrome is caused by a mutation of SRY (sex-determining region of the Y chromosome) and other mutations associated with testicular formation (desert hedgehog *DHH*, steroidogenic factor 1, *NR5A1*, *WNT4*, *DAX1*) (Das et al. 2011). Patients with Swyer syndrome have streak gonads, which do not produce androgens or antimüllerian hormone. This leads to a female phenotype and müllerian structures, as well as female external genitalia. Clinical presentation is usually primary amenorrhea and possibly delayed puberty. Upon diagnosis of Swyer syndrome, it is recommended that streak gonads be removed given the increased risk of malignancy in the testicular portion of the gonads. The incidence of malignancy is up to 20–30% and includes gonadoblastoma, dysgerminoma, endodermal sinus tumor, choriocarcinoma, and embryonal carcinoma (Cools et al. 2006).

Exogenous hormonal therapy can be given for sexual maturation with a similar regimen for Turner syndrome. These patients will also have infertility, but can undergo in vitro fertilization with oocyte donation. There is no other special screening or health monitoring needed.

22.1.5 46,XX Gonadal Dysgenesis

Gonadal dysgenesis can also present with a normal 46,XX karyotype, due to some autosomal gene defects that encode for nucleic acid binding proteins and transcription factors involved in oogenesis (Simpson 2008). Patients may present with primary amenorrhea but will have normal height and sex characteristics.

22.1.6 Fragile X Premutations (FMR1)

It is recommended that women diagnosed with diminished ovarian reserve and primary ovarian insufficiency (cessation of normal ovarian function before age 40 years) should be screened for fragile X (ACOG 2006). The prevalence of POI in fragile X carriers lies somewhere between 10% and 20% (Davidson et al. 2000). In fact, some argue that any female should be screened, particularly when considering pregnancy as the sensitivity is high ~99% and there are implications to offspring health. This disease is a result of an *FMR1* gene mutation on the X chromosome at Xq27.3 leading to expanded CGG repeats. $>$40–55 CGG repeats indicate intermediate expansion, $>$55 to $\leq$200 repeats indicate fragile X (alphabetical X) premutation carrier status, and $>$200 repeats are considered the full mutation. In boys, clinical features encompass a wide range including developmental delay, intellectual disability, language, math, visuospatial, and attention deficits.

Physical findings range widely and may include relative macrocephaly, pale blue iris, strabismus, arched palate, mitral valve prolapse, joint hyperlaxity, hypotonia, and flexible flat feet. In females, full mutations can lead to milder effects on cognitive and behavioral development and intellectual disability. With the permutation, women can present with primary ovarian insufficiency, later onset of fragile x-associated tremor-ataxia syndrome, and milder cognitive deficits. Women with POI and the fragile X mutation

should be counseled regarding the decreased fertility potential, as well as the possibility of passing the mutation onto their offspring. In vitro fertilization with preimplantation genetic diagnosis should be discussed with women as part of the counseling.

22.2 Normal Chromosomes

22.2.1 Autoimmune POI

About 3% of patients with POI will have concurrent diagnosis of adrenal insufficiency (Bakalov et al. 2002). If a POI patient has a normal karyotype, then workup for autoimmune etiologies for POI is warranted as the next step.

> Suspicion for autoimmune POI should be higher in a patient with a family history of autoimmune disease, or personal history, such as hypothyroidism, diabetes mellitus, pernicious anemia, myasthenia gravis, and hypoparathyroidism.

Although tests for anti-ovarian antibodies exist, these tests can be inconsistent, and there is no clear indication for testing given these findings (Novosad et al. 2003). Since a diagnosis of adrenal insufficiency would affect future medical management, testing for adrenal antibodies is reasonable. In fact, women that test positive for antibodies will have a 50% risk of developing adrenal insufficiency (Betterle et al. 1997). Anti-adrenal or 21-hydroxylase antibodies can be ordered to screen for the majority of causes for autoimmune POI, although defects in other steroidogenesis enzymes are rarer causes. Other screening labs include TSH, free T4, anti-thyroperoxidase (TPO) antibodies, and a CMP to evaluate calcium, phosphorus, and fasting glucose. If there is a positive result for an adrenal antibody, providers should pursue confirmatory testing for adrenal insufficiency with ACTH stimulation test.

22.2.2 Other Etiologies for POI

Occasionally, the workup for POI will reveal normal karyotype, fragile X testing, and no evidence of autoimmune antibodies. There are other genetic defects that may contribute to POI, and next-generation sequencing to identify these potential mutations is being investigated but is not practiced routinely in the clinical setting. Mutations such as *FSHR*, *LHCGR*, *FOXL2*, *BMP15*, *STAG3*, *NOBOX*, *FIGLA*, and *STAG3* have been identified as nonsyndromic causes for POI. Advances are being made with new technologies like next-generation screening in identifying putative genes in POI (Fonseca et al. 2015).

22.2.3 Radiation

Radiation therapy (RT) may induce primary ovarian insufficiency, depending on the age, radiation dose, and radiation field. A later age of exposure, higher dose, and abdominal/pelvic radiation provide higher risk for POI. A dose of 2 Gy to the ovary will leave approximately 50% oocytes to survive (Wallace et al. 2003). Survivors after RT are at increased risk of POI and its subsequent long-term effects on bone and cardiovascular health. To decrease the risk of ovarian failure, ovarian shielding and surgical transposition of the ovaries prior to treatment are options. Success rates vary with radiation dose and field, as ovaries may be affected by scatter radiation or adjuvant chemotherapy. In patients who are anticipating undergoing radiation therapy, counseling for fertility preservation is important, particularly for IVF with oocyte or embryo cryopreservation. In prepubertal females, the only option that currently exists is ovarian tissue cryopreservation, which is experimental in nature and done primarily in the clinical setting.

22.2.4 Chemotherapy

Chemotherapy can cause DNA damage in oocytes, leading to apoptosis, and accelerated depletion of the primordial follicle pool. Exposure to chemotherapy can predispose women to primary ovarian insufficiency. The type, duration, and age at exposure can influence the toxicity, with an increasing risk associated with an increasing age of exposure (Sonmezer and Oktay 2004).

Table 6 HRT regimens for premature ovarian insufficiency (higher doses in younger versus older)

Estrogen regimen options	Progestin regimen options
Transdermal estradiol 100–150 mcg daily (patch dosing 1 or 2× per week)	Oral medroxyprogesterone acetate 10–40 mg daily × 12 days per month
2 mg oral micronized estradiol daily	Micronized progesterone 200 mg daily for 10–12 days per month
1.25 mg oral conjugated equine estrogen daily	Combination products: conjugated equine estrogen 1–2 daily – 0.45/1.5 or 0.625 mg/2.5 mg
1.25 mg oral esterified estrogen daily	

Studies have looked at GnRH agonists for ovarian protection during chemotherapy, with mixed results. This is not currently recommended for fertility preservation based on a recent systematic review; however, there are studies showing some benefit in the breast cancer population (Elgindy et al. 2015; Moore et al. 2016). Patients undergoing chemotherapy should be referred to a reproductive endocrinology and infertility specialist to discuss fertility preservation options, including in vitro fertilization with oocyte or embryo cryopreservation. Ovarian tissue cryopreservation is an option for prepubertal girls, which is still being investigated in clinical research trials.

There are special ovarian stimulation protocols that are safe for women with estrogen-sensitive tumors.

22.2.5 Galactosemia

Galactosemia is an autosomal recessive disorder, where patients are unable to metabolize galactose due to galactose-1-phosphate uridyl transferase deficiency. Galactose metabolites may cause damage to germ cells migrating to the genital ridge in the developing embryo (Levy et al. 1984). Typically this diagnosis is made in young children or neonates due to developmental and growth delays or failure to thrive with milk intake.

22.2.6 Resistant Ovary Syndrome

This rare syndrome presents clinically with amenorrhea, possibly delayed puberty, elevated gonadotropins, and presence of ovarian follicles. The etiology may include defective or absence of gonadotropin receptors or intracellular downstream signaling defects.

22.2.7 17-Hydroxylase Deficiency

This presents with delayed puberty (no sexual characteristics because sex steroid production is impossible), hypertension, hypokalemia, and elevated progesterone levels.

22.2.8 Follicular Development Failure

Genetic defects in follicular development may contribute to POI. Genes encoding for folliculogenesis, steroidogenic enzyme synthesis, gonadotropin receptor signaling, and intracellular signaling may contribute to some of the pathways not clearly defined leading to POI. Some of the genes include steroidogenic acute regulator enzyme (*STaR*) and aromatase (*CYP19A1*).

22.2.9 Counseling and Management of POI

POI patients should be counseled that they might still have intermittent ovulation and menses. Patients not interested in having children should use contraception. Patients desiring future fertility should be counseled that about 10% of women with POI have spontaneous conception and if they achieve a pregnancy, 80% will lead to a healthy live birth (Van Kasteren and Schoemaker 1999). The physician should discuss long-term outcomes and pregnancy chances with patients. Given that they are at higher risk for diminished ovarian reserve-related infertility, they should seek infertility guidance sooner than the 1 year of attempted conception and consider IVF with donor oocyte to improve their success rates.

One of the main adverse effects of POI is the elevated risk of developing osteopenia and osteoporosis (Gallagher 2007). Early menopause is also

an independent risk factor for developing cardiac disease (Atsma et al. 2006). In addition, vasomotor symptoms, urogenital atrophy, and other associated findings with menopause may greatly affect quality of life. Treatment with exogenous estrogen therapy is recommended unless there is a contraindication. Treatment to achieve physiologic doses of estradiol (approximately 104 pg/mL or 382 pmol/L) should continue until at least 50 years old, after which women can be transitioned to menopausal level hormone therapy (Mishell et al. 1971) (Table 6).

22.2.10 Pituitary Disorders

In patients with low estradiol and low-normal gonadotropin levels, one must be suspicious for hypothalamic or pituitary failure. Imaging of the sella turcica is recommended to rule out any intracranial pathology. CT and MRI with a special view on the sella turcica are both reasonable options. MRI is the more sensitive imaging modality, provides the least radiation exposure, and can better characterize the sella and suprasellar regions and distinguish between solid tumors and vascular abnormalities, including hemorrhage. However, MRI can be lengthy and is much more expensive, so it is reasonable to pursue CT in certain contexts.

22.2.11 Pituitary Adenomas

Pituitary adenomas are largely benign and are the most common etiology for amenorrhea caused by a mass in the anterior pituitary. They are typically monoclonal (of one cell type) and may or may not be functional. They are classified as microadenomas if they are less than 10 mm and macroadenomas if they are greater than 10 mm. They may present with amenorrhea, galactorrhea, or neurologic symptoms such as headache and visual impairment, with the most common being bitemporal hemianopsia (from compression of the optic chiasm) or diplopia.

22.2.12 Lab Testing

In addition to imaging, laboratories are indicated to assess pituitary function as deficiencies may affect a patient's health.

If a patient has amenorrhea, the initial endocrine workup includes TSH, prolactin, FSH, and estradiol.

If there are findings of a macroadenoma on imaging, we recommend drawing a free T4 to distinguish between primary and secondary hypothyroidism, IGF-1 to evaluate for growth hormone deficiency, and morning cortisol drawn between 6am and 9am to screen for adrenal insufficiency.

- In the setting of low cortisol levels, ACTH stimulation test is indicated. Cosyntropin is administered (0.25 mg) IM or IV, with subsequent measurement of serum cortisol before and 60 min after mediation is administered. Normal levels post-administration are $\geq$15–18 μg/dl. Elevated basal cortisol may indicate Cushing's syndrome and requires further workup. Lack of response (i.e., if cortisol does not rise with cosyntropin administration) indicates that the adrenal gland is likely atrophic from chronic ACTH deficiency.

22.2.13 Gonadotroph Adenomas

Gonadotroph adenomas are typically nonfunctional and make up the majority of benign inactive adenomas in the pituitary. They often present with neurologic symptoms of headache and visual changes. Most patients have normal or low gonadotropin concentrations on workup. In rare cases, FSH-secreting tumors can cause spontaneous ovarian hyperstimulation syndrome. They may also cause ovarian cyst formation, amenorrhea, and premature breast development and bleeding in prepubertal girls. They mechanism for causing amenorrhea is through compression of the pituitary stalk, interrupting dopamine, leading to increased prolactin secretion. Gonadotroph adenomas may secrete a-subunit, and levels may be elevated on testing. There is no standard medical treatment for functional gonadotroph adenomas, and GnRH agonist has not been successful in downregulating FSH or LH in these cases.

Surgical treatment through transsphenoidal resection is an option, but it has its own risks and may potentially lead to removal of functional pituitary tissue.

22.2.14 Thyrotroph Adenomas

Functional thyrotrophs are rare and present with symptoms of hyperthyroidism. This includes fast heartbeat, palpitations, heat intolerance, nervousness, weight loss, hunger, insomnia, and more. They may also develop a goiter and have oligo- or amenorrhea, galactorrhea, and other neurologic symptoms. These patients will have a wide range of TSH levels and high levels of free T4 and T3, as well as elevated free a-subunit. Treatment is recommended and includes transsphenoidal resection and octreotide if there is persistent tumor (or sometimes is used preoperatively). Octreotide is a somatostatin analog and can reduce TSH levels.

22.2.15 Somatotroph Adenomas

Functional somatotroph adenomas lead to excess secretion of IGF-1 and lead to acromegaly. Symptoms and signs are typically gradual in onset and may include large hands and feet, enlarged jaw, deepening voice, fatigue, weakness, headache, and visual changes. IGF-1 level has diurnal variation and is age-specific. An oral glucose tolerance test can be used to diagnose acromegaly. Growth hormone levels will be low in normal individuals 2 h after 75 g glucose tolerance test (GTT) but in acromegaly will continue to be elevated ($>$0.3 ng/mL). The recommended treatment is transsphenoidal surgery that has good outcomes and leads to an 80–90% rate of resolution. If there is still a persistent functional tumor after removal, then octreotide is administered.

22.2.16 Corticotroph Adenomas

Cushing's disease is the most common manifestation of functional ACTH-secreting corticotroph adenomas. Clinically, high levels of cortisol lead to the "Cushing's" phenotype of facial and central adiposity, abdominal striae, nuchal fat/buffalo hump, and some hyperpigmentation. Many of these patients will have amenorrhea, hirsutism, and acne. Different methods for diagnosis include 24 h urinary free cortisol, dexamethasone suppression test, and salivary cortisol test. With the overnight dexamethasone suppression test, 1.0 mg dexamethasone is given late (between 11pm and midnight), and serum cortisol is measured the following morning around 8am. Values of $\geq$1.8 mg/dl are abnormal. If one test is abnormal, we recommend a second test to validate the findings. Treatment for corticotroph adenomas is resection via transsphenoidal surgery, followed by radiation therapy for those that have persistently elevated cortisol after surgery. If radiation therapy fails, adrenalectomy is an option for definitive treatment, but has its own risks.

22.2.17 Lactotroph Adenomas (Prolactinoma)

Forty percent of pituitary adenomas are prolactinomas. They may spontaneously occur or be part of a syndrome called MEN1 (multiple endocrine neoplasia type 1), as a result of a *MEN1* mutation. Clinical manifestations include amenorrhea and galactorrhea, and in prepubertal patients severe cases may impair growth. Patients with prolactinomas have elevated prolactin levels, which tend to correlate with the size of the mass. If the adenoma is part of MEN1, patients can have hyperparathyroidism and hypercalcemia. Occasionally patients will have elevated IGF-1, since up to 10% of prolactinomas produce growth hormone.

Lactotroph microadenomas are common, rarely progress beyond 1 cm, and are typically not changed with medical therapy such as dopamine agonist. They often recur even if they are resected, but they often do not have any adverse health effects. Repeat imaging for microadenomas can be done at 1, 2, and 5 years after diagnosis. If there is no change in symptoms or mass size, then surveillance imaging can be discontinued.

If there is a presence of a macroadenoma and prolactin levels are $<$100 ng/mL, it is likely another type of secreting adenoma, and/or the macroadenoma is causing stalk compression and disruption of the dopamine regulation of prolactin. Commonly these tumors are associated with irregular menses or CNS symptoms, such as headaches or visual disturbances. Referral should be

made to neurology and neurosurgery for further consultation and management. If a patient has a macroadenoma and prolactin levels >100 ng/mL, the diagnosis of prolactinoma is most likely. Growth of these tumors is typically slow but warrant management with an endocrinologist or reproductive endocrinologist, neurologist, and neurosurgeon for multidisciplinary management. If a patient is asymptomatic, long-term surveillance is reasonable, and repeat imaging should be done at 1/2, 1, 2, and 5 years. Any growth or CNS symptoms warrant treatment. In addition, endocrine screening of TSH, prolactin, IGF-1, and 24 h urinary cortisol or dexamethasone suppression test are recommended.

22.3 Treatment

22.3.1 Medical Therapy

Medical therapy for prolactinomas can be tailored to a patient's goals and is detailed above under hyperprolactinemia. If the patient does not desire pregnancy and does not have neurologic symptoms, she may use hormonal contraception for regulation of menses and pregnancy prevention. In patients desiring restoration of menses or desire pregnancy, the initial treatment for functional symptomatic prolactinoma is a dopamine agonist, which includes bromocriptine and cabergoline and is detailed above in the Sect. "11.5." Both bromocriptine and cabergoline are safe for conception and pregnancy and typically restore ovulation and menstrual function once prolactin levels resolve.

After initiating medication, prolactin levels should be checked 2–3 weeks later as they should normalize in weeks. Medical therapy may also work for symptomatic macroadenomas, but may take longer than the response seen with microadenomas. After initiation of treatment, repeating the MRI to assess size in macroadenomas after 3–6 months can help assess response. If a tumor is stable in size during treatment, it may be a nonfunctional adenoma.

For microadenomas, the dose of dopamine agonist can be reduced after a year and even discontinued if the prolactin levels normalize for >2 years and repeat MRI is negative for an adenoma.

Macroadenomas: During therapy, a repeat MRI after 6 and 12 months of treatment is recommended. DA therapy can be reduced if the macroadenoma has decreased in size and the prolactin level is normal for >1 year. If the prolactin level is normal for 2 years and the MRI shows minimal or no evidence of tumor, the treatment can be reduced and possibly stopped. Levels and symptoms must still be followed for possible recurrence or regrowth.

22.3.2 Surgical Therapy

Transsphenoidal resection of macroadenomas is an option for large tumors (especially those seeking to get pregnant) or failure to respond to medical therapy. Incomplete resection is common; thus often patients may need further therapy.

22.3.3 Radiation Therapy

Radiation therapy is used for patients who underwent surgery for large macroadenomas with a persistent sizable tumor. Radiation therapy puts patients at risk for panhypopituitarism over 10 years after treatment (Snyder et al. 1986).

22.3.4 Fertility and Pregnancy

With dopamine agonist treatment, 80% of patients can achieve spontaneous ovulation and pregnancy (Kupersmith et al. 1994). The risk of microadenoma growth in pregnancy due to elevated estrogen levels is only 1–2%, and 5% will have some growth without symptoms. However, in patients with macroadenomas, growth and symptoms may occur in 15–20% (Molitch 1999). Dopamine agonist is discontinued during pregnancy, and it is not necessary to rechecking prolactin during pregnancy. If a patient develops neurologic symptoms secondary to an adenoma, a dopamine agonist can be safely given in pregnancy. Prolactin levels can be checked 2 months postpartum. DA therapy should not be given while breastfeeding. Reassuringly, there are no effects of breastfeeding on growth in micro- or macroadenomas. If patients are symptomatic

when they deliver, they should not breastfeed as medical or surgical treatment may be indicated.

22.3.5 Empty Sella Syndrome

Empty sella syndrome occurs due to removal/destruction of a pituitary adenoma leading to filling of the sella with cerebrospinal fluid. In rare cases, it may present as a congenital finding. Asymptomatic patients who have elevated prolactin levels and an "empty sella" on MRI should have annual surveillance with prolactin and MRI.

22.3.6 Sheehan Syndrome

Sheehan syndrome is caused by ischemia of the anterior pituitary usually due to an acute blood loss such as that from postpartum hemorrhage. Clinically, it presents as difficulty with postpartum lactation, but may result in panhypopituitarism with endocrine deficiencies manifesting as fatigue, anorexia, weight loss, and amenorrhea. A laboratory workup to assess the pituitary function is important, including TSH, IGF-1, cortisol, and FSH/LH. Electrolytes should be checked as patients may concomitantly have hyponatremia. ACTH stimulation test should not be done until 6 weeks after initial event, as the adrenal gland may not have had chronic-deficient exposure to ACTH too soon after.

22.4 Infiltrative Lesions

22.4.1 Hemochromatosis

Hereditary hemochromatosis is caused by a mutation in the *HFE* gene, which encodes for a protein expressed on the cell surface that interacts with transferrin and affects regulation of iron levels. In hemochromatosis, serum iron levels will be elevated due to increased absorption in the gastrointestinal tract, and iron overload can lead to damage to different tissues/organs. Fasting transferrin saturation (serum iron: total iron binding capacity) will be >45%, and serum ferritin >300 μg/L is an abnormal finding. Affected patients should be sent for HFE genotype. Sometimes, liver biopsy is performed to assist with diagnosis. Treatments include phlebotomy and chelation therapy.

22.4.2 Lymphocytic Hypophysitis

Lymphocytic hypophysitis is an autoimmune disorder that causes inflammation and damage to the pituitary. It most commonly occurs in pregnancy and postpartum and may be accompanied by hyperprolactinemia and hypopituitarism. Treatment may include transsphenoidal surgery, dopamine agonists, immunosuppression, or pituitary radiotherapy.

22.4.3 Hypogonadotropic Hypogonadism:

The constellation of amenorrhea, normal imaging, low estradiol, and low or normal gonadotropins may be classified as hypothalamic amenorrhea. This diagnosis can be made after excluding other potential etiologies for amenorrhea.

22.5 Hypothalamus

22.5.1 Hypothalamic Amenorrhea

Factors associated with functional hypothalamic amenorrhea (FHA) include low body weight, decreased nutritional intake and/or eating disorders, excessive or frequent exercise, and emotional stress. Sometimes it is found in patients with none of the above. In FHA excessive stress or malnutrition is thought to alter the GnRHI pulsatility, leading to no or low gonadotropin production or release of gonadotropins with decreased functional activity. Increased levels of endorphins, corticotrophin-releasing hormone, ACTH, and cortisol cause a decrease in the amplitude and frequency of GnRH. Often, alterations in diet, lifestyle, and life stressors can reverse FHA and lead to resumption of menses.

22.5.2 Eating Disorders

There are ranges of eating disorders that can lead to amenorrhea.

Anorexia nervosa is an eating disorder with DSM-5 diagnostic criteria:

1. Restriction of energy intake relative to requirements leading to significantly low body weight in the context of age, sex, developmental trajectory, and physical health

2. Intense fear of gaining weight or becoming fat even through underweight
3. Disturbance in the way which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight

Anorexia can result from restriction of calories and binging/purging with the use of laxatives/diuretics. Physical exam and laboratory findings may include lanugo (thin hair covering body), bone density loss, anemia, renal failure, and amenorrhea.

Patients have low FSH, LH, estradiol, IGF-1, and leptin. Cortisol levels may be elevated, and thyroid studies are often normal. Treatment involves intensive nutritional, medical, and cognitive behavioral therapy. Patients may require hospitalization for severe electrolyte derangement and dehydration.

Bulimia nervosa has DSM-5 diagnostic criteria and is defined as:

1. Having recurrent episodes of binge eating in which large amounts of food are consumed in a discrete amount of time (<2 h) and a sense of lack of control over eating.
2. Recurrent inappropriate compensatory behavior in order to prevent gaining weight (i.e., purging).
3. Binge eating and compensatory behaviors both occur at least 1×/week for at least 3 months.
4. Self-evaluation is influenced by body shape and weight.
5. Disturbance does not occur exclusively during episode of anorexia nervosa.

Patients with bulimia may have electrolyte imbalances, tooth and gum decay, chronic constipation/irregular bowel movements, and renal insufficiency.

22.5.3 Exercise

The combination of intense exercise, low body fat, and weight loss leading to a negative energy balance can lead to amenorrhea. The degree of amenorrhea is associated with the intensity of exercise. Running, gymnastics, and dance are activities where lean body mass is valued but is associated with higher rates of amenorrhea. In exercise-induced HA, decreased GnRH pulsatility and impaired gonadotropin release are thought to stem from adrenal activation (cortisol and CRH), endogenous opioid release after exercise, and decreased circulating leptin levels. Workup of HA should include the general workup for amenorrhea – HCG, LH, FSH, prolactin, and TSH. In suspected cases of exercise-induced amenorrhea, vitamin D levels and DEXA scan should be ordered. Generally blood results include normal TSH and prolactin levels, along with low-normal levels of gonadotropins and hypoestrogenism.

The "female athlete triad" refers to women with menstrual dysfunction, low calorie intake, and low bone density. The hypoestrogenism from HA leads to decreased trabecular bone density and can predispose women to stress fractures. In addition, weight-bearing activity does not negate the negative effects of low estrogen on bone health. Lifestyle changes including increasing nutritional intake and decreasing exercise intensity provide the best benefits toward improving bone density and restoration of menstrual function. Exogenous hormonal therapy may be indicated in cases of osteopenia where lifestyle changes do not improve bone density or the patient does not wish to engage in lifestyle changes. Supplementation with calcium (1,000–5,000 mg per day) and vitamin D (1,000–2,000 IU per day) is encouraged but not sufficient to restore and maintain bone density if hypoestrogenism is not corrected. In addition to effects on bone, hypoestrogenism may predispose women to higher levels of total cholesterol, triglycerides, and LDL. For patients seeking pregnancy who do not have resumption of menses after lifestyle changes, gonadotropin use for ovulation induction may be necessary.

22.6 Congenital GnRH Deficiency

GnRH deficiency is a genetic cause of hypothalamic amenorrhea. It can be inherited in autosomal dominant, autosomal recessive, and X-linked

fashions. The majority of etiologies are sporadic, but many patients will have a family history of delayed puberty or infertility. Below are the different etiologies for GnRH deficiency.

22.7 Kallmann's Syndrome

Kallmann's syndrome is a disorder characterized by congenital GnRH deficiency and anosmia (or hyposmia). It is believed to arise from genetic mutations that affect GnRH neuronal migration to the ventral hypothalamus as well as olfactory neuron migration. Anosmin, an amino acid cell adhesion protein encoded by KAL1, is improperly expressed, leading to defunctory migration. FGFR1 mutations are autosomal dominant and are loss-of-function mutations, affecting signaling of fibroblast growth factor. The different genes include fibroblast growth factor-1 receptor (*FGFR1* – autosomal dominant), KAL gene (*Kal1* – X-linked), *FGF8*, *PROKR2*, *KAL3*, *KAL4*, and *KISS1*. Patients typically present with primary amenorrhea and delayed growth/puberty, but there are variations in severity. A unique finding in Kallmann's syndrome is that patients do go through adrenarche and thus have normal pubic hair. They have some DHEAS production and small amount of adrenal androgen and estrogen production. Patients may have other findings such as clef palate or lip, syndactyly, and other genitourinary anomalies.

The following labs can be drawn, and these cutoffs are typically found in GnRH deficiency: estradiol <20 pg/mL, FSH and LH low (<4–5 IU/L each), and normal pituitary function (TFTs, cortisol, IGF1, and imaging findings w/o evidence of pituitary mass).

22.8 GnRH Receptor Mutations

There are several mutations that inactivate the GnRH receptor gene, affecting GnRH binding, transport, etc. The clinical presentation ranges from puberty delay to not having development of secondary sex characteristics. Other genes involved include *GnRHR*, *GnRh1*, *TAC3*, *TAC3R*, *CHD7*, and *Semaphorin 3A.*

We recommend treatment of GnRH deficiency with hormone replacement therapy. The regimen depends on the severity and current age of the patient and includes bone age, height percentile, predicted adult height, and desired psychosexual outcomes. The goal is to help achieve secondary sex characteristics, build bone and muscle mass, and sustain/restore fertility. Treatment with oral or transdermal estradiol starting at low doses will initiate breast development. The dose is gradually increased to complete sexual maturation once breast development and a reasonable height are attained. After this, long-term combination oral contraceptives or replacement therapy to 50 and possibly beyond is recommended.

22.8.1 Dosing

Transdermal: 0.08–0.12 mcg estradiol per kg body weight.

Oral CEE: 0.3 mg per day up to 1.25 mg per day.

Once menses initiates, then addition of cyclic progestin therapy is indicated to protect against endometrial hyperplasia.

Patients with GnRH deficiency desiring fertility will need exogenous gonadotropins in order to induce ovulation.

23 Conclusion

The basic workup for amenorrhea includes hCG to exclude pregnancy, followed by TSH, and prolactin in nonpregnant women. FSH can be checked to evaluate the hypothalamic-pituitary axis. The most common reason for amenorrhea is ovarian dysfunction. With a normal FSH, PCOS, thyroid dysfunction, and hyperprolactinemia are the most common reasons for abnormal menses. High gonadotropins are concerning for primary ovarian insufficiency. The most common etiologies for this are genetic, and karyotype and fragile X should be evaluated

in the initial step, followed by an autoimmune workup. In patients with a low FSH, a hypothalamic etiology must be evaluated and imaging obtained to rule out pituitary mass. In patients with low BMI weight loss, stress, or vigorous exercise, hypothalamic amenorrhea is common. Congenital outflow abnormalities can be detected with a physical exam and pelvic ultrasound and are seen with primary amenorrhea. In patients with a history of uterine instrumentation, Asherman should be suspected and can be evaluated with sonohysterography or hysteroscopy.

24 Cross-References

- Congenital Anomalies of the Reproductive Tract
- Hyperprolactinemia, Galactorrhea and Pituitary Adenomas
- Workup and Management of Polycystic Ovary Syndrome

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Office Procedures: Endometrial, Cervical, and Vulvar Biopsy

Donna Shoupe

Contents

Abstract

Bleeding abnormalities along with disorders of the uterus, cervix, and vulva are common causes for outpatient visits to the gynecologist. Most of these disorders are benign in nature, but it is the job of the examining physician to establish the severity of the disorder by distinguishing benign versus more serious lesions. In addition, the biopsy, in many cases, will establish a specific diagnosis and direct treatment options.

Keywords

Endometrial biopsy • Cervical biopsy • Vulvar biopsy • Cervical lesion • Abnormal uterine bleeding • Vulvar lesion • HPV

1 Introduction

In-office gynecologic procedures are now a mainstay of women's healthcare. Biopsies of the endometrium, cervix, and vulva can be safely done in the office, and they usually allow the woman to quickly resume her normal activities. The biopsy is primarily done to exclude the diagnosis of cancer and potentially establish the diagnosis and treatment options.

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2 Endometrial Biopsy

2.1 Evaluation

It is estimated that one-third of outpatient gynecologic visits yearly in the USA are for abnormal uterine bleeding (Awwad et al. 1993; Cooper 2000). Differential diagnosis of abnormal uterine bleeding includes anovulation, leiomyoma, polyps, endometrial hyperplasia, cancer, medications, and coagulation disorders (Table 1). Women with abnormal bleeding are at risk for anemia and disability from heavy bleeding, and they may suffer occupational, sexual, social, or psychological impact. In most cases, management of abnormal bleeding can be handled on an age-specific basis in an outpatient setting, often starting with an endometrial biopsy. Abnormal genital bleeding can also originate from the vulva, vagina, and cervix.

Evaluation of the patient presenting with abnormal uterine bleeding starts with a detailed history of the patient's normal bleeding pattern, time when abnormal bleeding began, and pattern and quantity of bleeding. Additional details should include associated symptoms, current and past medical problems, and medication history. Gynecologic history should include last Pap test, any prior endometrial biopsy or dilation and curettage, known fibroids, and prior ultrasound results. Vital signs, height and weight, and general physical exam are important. Evaluation of the skin for bruising or petechiae, conjunctiva, thyromegaly, galactorrhea, and evidence of androgen excess can suggest etiology of abnormal bleeding. An abdominal exam should evaluate for signs of infection, trauma, distention, guarding, abdominal mass, or ascites. A pelvic exam should check for vulvar, vaginal, or cervical lesions; determine size and shape of the uterus; quantify bleeding; identify masses and tenderness; and establish that bleeding is coming from the cervical os or vaginal trauma. In reproductive-age women at risk for pregnancy, a pregnancy test should be done (Table 2).

Table 1 Causes of abnormal uterine bleeding

Uterine etiology	*Medications*
Leiomyoma, adenomyosis	Contraceptives, hormone replacement
Polyp	Psychotropic drugs, MAO inhibitors
Endometrial hyperplasia, cancer	Anticoagulants
Infection: endometritis	SERMs
Congenital anomalies	Corticosteroids
Vascular lesions, hemangioma	Chemotherapeutic agents
Atrophic endometrium	Dilantin, digoxin
Systemic etiology	*Other*
Liver disease	Anovulation, PCO
Thyroid disorders	Perimenopausal transition, perimenarchal DUB
Adrenal disorders, late-onset CAH	Pregnancy, accidents of pregnancy
Leukemia, thrombocytopenia	Lactation, hyperprolactinemia
Thrombophilias [von Willebrand's disease]	Foreign body, trauma
Ovarian tumors	

An endometrial biopsy is often an important first test for women over 35 with irregular bleeding [metrorrhagia] or heavy bleeding [menorrhagia], women under 35 with long-standing abnormal bleeding > 6–12 months, and women with postmenopausal bleeding. In addition to identifying neoplasia or malignancy, an endometrial biopsy can provide useful information regarding ovulatory status when secretory endometrium is identified or in diagnosing chronic endometritis. For persistent bleeding, adjunctive testing may be indicated (Table 3). Ordering of adjunctive testing depends on the age of patient, length of time and heaviness of abnormal bleeding, gynecologic history, prior imaging results, medical conditions, contraceptive or hormonal use, other medications, size of the uterus, the presence of androgen, or steroid excess. Acute heavy bleeding may need acute surgical intervention or transfusion.

2.2 Contraindications

The presence of a viable and desired pregnancy is the only absolute contraindication to endometrial biopsy. Caution should be used when considering

Table 2 Etiology of abnormal uterine bleeding by age groups

Childhood < 10 years	
	Newborn withdrawal from placental hormones
	Foreign objects
	Vaginitis
	Trauma
	Sexual abuse
	Ovarian tumor [with secondary sexual characteristics
	Contraceptive pill/HRT/hormonal ingestion
	Precocious puberty
Adolescents 10–18 years	
	Physiological anovulation [2–3 years after menarche
	Coagulation defect, thrombophilia [von Willebrand's disease]
	Thrombocytopenic purpura
	Leukemia, aplastic anemia, hypersplenism
	Platelet dysfunction from medications
	Premature ovarian failure, gonadal dysgenesis
	Congenital reproductive tract anomalies
	Medications: hormones, anticoagulants, chemo
	Systemic disease: thyroid, liver, adrenal
Reproductive 19–39 years	
	Pregnancy-related complications
	Anovulation, PCO
	Fibroids [particularly submucous], polyp
	Medications: hormones, anticoagulants, chemo, psychoactive
	Systemic disease: thyroid, liver, adrenal
	Endometrial hyperplasia [rare cancer]
Late reproductive 40–49 years	
	Perimenopausal transition, anovulation
	Leiomyoma [particularly submucous], adenomyosis
	Endometrial polyp
	Medications: hormones, anticoagulants, chemo, psychoactive
	Systemic disease: thyroid, liver, adrenal
	Endometrial hyperplasia, infrequent cancer
Menopausal 50 and above	
	Early menopausal transitional bleeding
	Hormone therapy
	Systemic disease: thyroid, liver, adrenal
	Medications: anticoagulants, chemo, psychoactive
	Endometrial hyperplasia, endometrial cancer
	Polyps, submucous leiomyomas

Cervical etiologies discussed in cervical biopsy sections

Table 3 Adjunctive testing: evaluation of abnormal bleeding [when indicated]

Transvaginal and transabdominal pelvic ultrasound [MRI, CT], hydrosonogram
Pap smear, gonorrhea, and *Chlamydia* screening
Hormone labs: **pregnancy test,** androgens, 17-hydroxyprogesterone, prolactin, progesterone, FSH, LH, estradiol
Other labs: CBC, liver function tests, thyroid function tests, renal function tests, ferritin glucose tolerance test, HgA1c, 24-hour urinary free cortisol, coagulation testing
Office or hospital hysteroscopy

a biopsy in women with bleeding abnormalities, severe liver disease, use of anticoagulation medications, acute cervical or pelvic infection, obstructing lesion, or cervical cancer. A low-suction pipelle device can generally be used safely in the presence of an intrauterine device.

2.3 Sampling Technique

An in-office endometrial biopsy is a relatively easy procedure, especially in young, parous women. An endometrial biopsy can be done with a variety of instruments including disposable low-pressure devices [pipelle catheter], or high-pressure devices [vacuum aspirating biopsy retrieval apparatus (VABRA), Karman cannula], or reusable low-pressure devices [metal pipette, Randall curette, Novak curette]. These methods collect strips or sections of the endometrium by suction and/or scraping of the endometrial surface. The pipelle is one of the most popular methods used. The outer diameter of the sheath is about 3 mm with a 2.1–2.4 mm opening at the distal end for collection of the sample. The sheath is made of flexible polypropylene, and it contains a firm plastic internal plunger that slides up and down. The pipelle samples only a small section of the endometrial surface, 4.5–15% (Eddowes 1990; Rodriguez et al. 1993; Guido et al. 1995). However, the pipelle is relatively easy to use, causes less pain, and is less expensive than the other methods that collect a larger proportion of the endometrial surface (Stovall et al. 1991; Silver et al. 1991). Importantly, the combined technique of using endometrial scraping or curettage, with a corkscrew twisting motion, is reported to result in a 95% success rate for obtaining adequate tissue for diagnosis (Sierecki et al. 2008). The recommendation is that even if an adequate sample was obtained, if bleeding persists, further evaluation is needed (Meniru and Hopkins 2006). Further evaluation may be necessary such as repeat pipelle sampling, ultrasound evaluation, VABRA, hysteroscopy, or dilation and curettage depending on clinical presentation and risk factors.

There is a 4–10% risk that cervical stenosis may interfere with getting the catheter through the cervical canal (Guido et al. 1995). In these cases, the use of either a disposable Os Finder or non-disposable dilators, 1–5 mm diameter, can be used to dilate the cervix in office. Pretreatment with vaginal or buccal misoprostol and/or NSAIDS may be helpful in patients with stenosis. The steps for an endometrial biopsy using a pipette are listed in Table 4. Rare complications include 0.1–0.2% perforation (Kaunitz et al. 1998; McElin et al. 1974; Leclair 2002), bleeding, vasovagal reaction, severe cramping during or after procedure, and infection. Desired pregnancy is a contraindication to endometrial biopsy. Relative contraindications include coagulation disorder, use of anticoagulation medication, and coagulopathy from other causes such as liver failure and endometritis. The use of prophylaxis antibiotics to prevent bacterial endocarditis is not required (Dajani et al. 1997).

There is also a disposable endometrial brush that is available. It is similar to the brush used for endocervical sampling. The use of the brush in addition to the endometrial low-pressure suction device was reported to result in a 100% specificity and diagnosis rate for hyperplasia or cancer (Del Priore et al. 2001).

2.4 Treatment Options

For younger women with anovulatory bleeding, treatment with the levonorgestrel-releasing IUD, combination of birth control pills or ring, or progestins can regulate and generally decrease menstrual flow. Younger women with hyperplasia without atypia can be appropriately treated with cyclic or continuous progestins. Pre- or postmenopausal women with hyperplasia with atypia should be referred to a gynecologist or gynecologic oncologist. Younger women with ovulatory bleeding should first be treated by addressing any clear structural or medical causes. After these problems are addressed, management may also include the levonorgestrel-releasing IUD; combination of oral contraceptive pills, ring, or patch; tranexamic acid; or nonsteroidal anti-inflammatory drugs (Sweet et al. 2012). Treatment for postmenopausal bleeding is also directed

Table 4 Steps for performing an endometrial biopsy

Consent signed and questions answered [consider vaginal or buccal Cytotec to soften the cervix the night before and morning of and/or 1 hour prior to procedure oral NSAID]	
Bimanual exam to establish size and position of the uterus	
Evaluation of the vulva and vagina and cervix for lesion; Betadine solution to clean the cervix	
Evaluate the cervical os and take note of possible stenosis, parous versus nonparous, amount of bleeding, and the absence of infection	
If there is stenosis of the cervix that prevents introduction of the biopsy catheter, dilation of the cervix may be necessary. The use of a tenaculum or paracervical block may facilitate this procedure	
There are multiple disposable as well as non-disposable dilators. A popular disposable dilator is the Os Finder. Having several dilation options available is helpful as the amount of beveling, diameter, and degree of flexibility of the dilator may play an important role in determining whether or not the dilation is possible. A very stenotic os requires a firm, tapered dilator to initiate the dilation, while canals that are very tortuous may need the more flexible and less pointed dilators	
When dilation is necessary or high-suction device is used, consider:	
1.	Paracervical block (prepackaged kits that include a needle guide and plastic needle spacer that control the depth of needle penetration
2.	Or 21–22 gauge [15 cm] extended length spinal needle
	10 ml syringe with a large 18–20 gauge needle to draw up 10–20 ml lidocaine, with or without epinephrine 1% or with vasopressin 3–5 units to 4:00 and 8:00 sites on the cervix; prior to injection, reverse pressure on the plunger to insure no backflow of blood, to avoid direct injection into the vessel
	Up to six sites on ectocervix, depth 3–7 mm
	Topical anesthetic cervical gels or creams can be used
Consider: Single-toothed tenaculum applied to upper cervix to stabilize the cervix and in some cases straighten out the cervix for easier insertion. After removal, insure hemostasis at sites of cervical perforation. Cotton tip swab can be pressed against any bleeding area with or without Monsel's solution. The use of a tenaculum and sound is standard when using a VABRA or high-suction device	
Insertion of uterine sound is not always necessary but can be used to establish a tract and measure the length of the uterus [generally 6–8 cm] and always used when using high-suction device	
Endometrial sampler is gently introduced into the uterine cavity; several passes are usually performed unless the patient is too uncomfortable to continue. The combined technique of endometrial curetting with a corkscrew twisting motion while using suction is recommended	
The sample is placed into specimen container and sent to pathology lab	
The presence of hemostasis insured	
Procedure note and orders entered into the chart	
Patient allowed to rest supine on the exam table for about 1–10 min after the procedure generally until moderate to severe cramping resolves. The patient should be then allowed to sit on the exam table, making sure she has no lightheadedness for 1–2 min before she stands up	
She should be counseled that although unlikely to happen, she should to return to clinic and seek medical help if she has fever, chills, continued cramping past 24–48 h, or abnormally heavy bleeding. The use of nonsteroidal anti-inflammatory drugs can be used during the day and before bedtime for moderate to severe cramping	

at the underlying cause, including removal of polyps or full evaluation of endometrial lesions by hysteroscopy, dilatation and curettage, or hysterectomy. Treatment options also include vaginal estrogen for vaginal atrophy, correction of systemic illness, or adjustment of hormone replacement therapy.

2.5 Complications and Side Effects

Cramping generally resolves within a few minutes of the procedure. The high-suction devices are associated with more cramping than the low-suction devices. After the procedure, patients should be encouraged to stay supine for a few minutes in order to avoid a vasovagal reaction. Rare complications include perforation, excessive bleeding, and infection. Unless prolonged dilation

is needed, a paracervical block is generally not needed. A paracervical block interrupts the sensory fibers of the cervix, upper vagina, and lower uterus. Intravascular injection or absorption of the anesthetic agent may cause headache, syncope, excessive sedation, or generalized convulsions.

3 Cervical Biopsy

3.1 Evaluation

Evaluation of the cervix is an integral part of the standard pelvic exam, and it includes both a visual and manual inspection as well as timely cervical cytology. Visual inspection of the cervix includes clear visualization of the cervical os, noting color changes, signs of infection, raised lesions, the presence of endocervical polyp or mass, trauma, foreign body, and discharge. The nonpregnant cervix is generally 2.5–3 cm in diameter and 3–5 cm in length. It is usually angled slightly backward and downward. The external cervical os in nonparous women is usually small and round, while in parous women there is often a transverse slit. The canal is approximately 8 mm wide and has longitudinal ridges. A cervical biopsy can either be a visually directed biopsy on the surface of the cervix using a cervical biopsy instrument or a blind scraping of the endocervical canal using an EndoCurette [endocervical curettage].

There are other types of cervical biopsies that are not covered in this chapter as they are often done in the operating room as an outpatient surgery. The loop electrosurgical excision procedure [LEEP] and various forms of cone biopsy procedures remove large, cone-shaped pieces of tissue from the cervix.

3.2 Differential Diagnosis

While most cervical biopsies are done as part of colposcopy for abnormal Pap smear or HPV testing, visual inspection of the cervix may reveal abnormal lesions that may warrant biopsy. The following are clinically significant cervical findings:

- Cervical or endocervical polyps are generally red, smooth, fingerlike growths often arising from within the cervical canal. The etiology of cervical polyps is not well understood, but they are likely due to estrogen stimulation of endocervical cells. Other possible etiologies include chronic infection or congestion of blood vessels. Cervical polyps are often asymptomatic but may cause bleeding or vaginal discharge. They can be very small, pea-sized, or large, several centimeters. While they are usually single, multiple cervical polyps can form. Removal of most cervical polyps is relatively simple and can be done in office using a ring forceps. Polyps with a thick diameter that originate deep within the cervical canal can be difficult to remove in office. Endometrial polyps can also extrude from the cervical os and are not easily distinguished from cervical polyps. There are a variety of histologic patterns that can occur: (1) typical endocervical polyp [mucosal], (2) granulation tissue, and (3) vascular, fibrous, pseudodecidual, endometrial or mixed endometrial and endocervical, and malignant area on part of polyp. The removal technique is described in Table 5.

Table 5 Steps in removing a cervical/endocervical polyp

Removal can usually be done by grasping the polyp with a ring forceps
The ring forceps are then twisted. The thicker the stalk, the slower the twisting to allow hemostasis at the base of the polyp. Polyps with a very thick stalk may require surgical removal
After removal of the polyp, the cervical os or base of polyp if visible should be checked for bleeding
If there is bleeding after the removal, a small Q-tip dipped in Monsel's solution can be placed into the cervical canal to the level of the base of the polyp. Good hemostasis should be insured
Specimen sent to pathology. Procedure note and orders entered into the chart
Although many of these removals are associated with minimal pain, patients with moderate to severe pain should be encouraged to stay in a supine position for a few minutes to avoid a vasovagal reaction

- Microglandular hyperplasia is a polypoid growth measuring 1–2 cm occurring most often in women on oral contraceptives or depot medroxyprogesterone acetate. It can also occur in pregnant or postpartum women. It is thought to be due to progesterone activity. Removal is the same as a typical cervical polyp (Table 5) (Nichols and Fidler 1971).
- Nabothian cysts are mucus-filled, firm cysts that appear on the surface of the cervix. They are thought to be caused when stratified squamous epithelium of the ectocervix grow over and cover the columnar epithelium of the endocervix. The result is that cervical crypts (usually 2–10 mm in diameter) are formed by trapped cervical mucus inside the crypts. Nabothian cysts, clearly seen as cysts filled with mucus, are benign and do not need to be biopsied.
- Currently, there are more than 40 HPV serotypes that can infect mucosal surfaces. Exophytic warts, from HPV 6 or 11, can occur on the vulva, vagina, and cervix, while flat warts on the cervix, from 16, 18, 31, 33, and 35, are associated with CIN. Pap testing now includes identification of the serotype of HPV present on the cervix. HPV is therefore associated with both flat and warty-like lesions on the cervix. The flat lesions are better visualized when treated with 3–5% acetic acid, which causes cellular dehydration and increased nuclear density and acetowhite appearance in dysplastic lesions. Lesions suggestive of HPV should be biopsied under colposcopic guidance for confirmation.
- Cancer generally will often appear as a friable ulcer or cauliflower-like growth. Biopsy of any raised or suspicious lesion on the cervix should be carefully considered. The technique for cervical biopsy is shown in Table 6.
- Squamous papilloma is a benign, small, solid, cervical lesion that commonly arises from inflammation or trauma. They are generally 2–5 mm in diameter. Treatment is removal (Table 6).
- Leiomyomas [smooth muscle tumors] may originate in the cervix accounting for about 8% of all uterine myomas. They are similar to lesions in the fundus but usually are small 5–10 mm in diameter. Removal can be performed with ring forceps if pedunculated (Table 5).
- Mesonephric duct remnants are usually located at the 3 or 9 o'clock position deep within the cervical stoma. These are remnants of the mesonephric or Wolffian ducts. They are usually only a few millimeters in diameter and usually incidental findings on 15–20% of sectioned cervices (Ferry and Scully 1990).
- Endometriosis is usually an incidental finding but may appear as a mass or cause abnormal or typically postcoital bleeding. It often appears as a bluish-black or bluish-red lesion 1–3 mm in diameter. Diagnosis is made by biopsy, often colposcopically directed biopsy (Phadins et al. 2005).
- Papillary adenofibroma is an uncommon neoplasm that appears as a polypoid structure. Similar growths may appear in the fallopian tubes or endometrium.
- Hemangiomas are also rare and similar to those found in the rest of the body. They can cause

Table 6 Techniques for cervical biopsy

Consents signed, questions answered
Area cleaned with Betadine or equivalent
Consider use of a tenaculum for stabilization of the cervix
Consider use of a local anesthetic injection [not typically done for in-office procedures]
Paracervical block [see above for technique]
Local injection under lesion
Cervical biopsy forceps used to remove lesion [under direct visual or using colposcopy]. Specimen placed in formalin and sent to pathology
Insure hemostasis following procedure using a long [Q-tip] cotton-tipped applicator [8 inches long], pressure for 30 sec–2 min or more
Addition of Monsel's solution applied to cotton-tipped applicator and placed directly with pressure at site of biopsy when necessary
Removal of tenaculum [if used] and careful to insure hemostasis at site of tenaculum puncture sites. Use of cotton-tipped applicators with or without Monsel's solution when necessary
Post-procedure patient counseling to avoid sex or anything in the vagina for at least 3 days. Report to clinic if heavy persistent bleeding, fever, and pain

vaginal bleeding or pain. The differential diagnosis included cervical cancer and treatment if surgical removal ((Gupta et al. 2006)–(Gusdon 1965)).

3.3 Contraindications and Complications

There are a very limited number of relative contraindications for cervical biopsy, and they are mainly various etiologies of active cervicitis. Although control of post-procedure bleeding with ferric subsulfate, Monsel's solution, silver nitrate, or pressure is very effective for most patients, a careful risk-benefit analysis is important in evaluating patients with known bleeding disorders, liver failure, or other coagulopathies. Generally, if colposcopy is done in a pregnant patient, biopsies, particularly endocervical curettage, are avoided.

Bleeding at the site of biopsy is the most common complication. Other complications include failure to biopsy the correct site or, rarely, post-procedure infection.

3.4 Follow-Up Care

Patients should avoid coitus, use of tampons, or any another intravaginal item for at least 3–14 days after the biopsy to allow healing. The patient should be instructed to return to the clinic or seek medical care if she experiences heavy prolonged bleeding, moderate to severe [worsening] pain over the next few days, or persistent fever.

4 Vulvar Biopsy

4.1 Evaluation

Symptoms related to vulvar lesions are common, often chronic, and can have a significant effect on a woman's sexual function, self-esteem, and quality of life. Inquiring about specific complaints as well as onset, duration, location, prior treatments, and any possible aggravating or precipitating factors is important in determining the etiology. Important past history includes childbirth, over-the-counter-treatments, cryotherapy, prior treatment for condyloma, vulvar laser, or prior vulvar biopsy or surgery.

The examination should begin with a thorough examination with good lighting. Adding colposcopic examination can often be helpful. Color changes, vaginal discharge, swelling, edema, visible lesions, tenderness, changes in architecture, fissures, and vascular lesions should be noted. These findings as well as size, nature of the border, contour, raised areas, and the presence of ulcerated areas should be accurately recorded. Biopsy of lesions showing hyperpigmentation, raised exophytic areas, changes in vascular patterns, or those that remain unresolved after treatment should be performed to rule out carcinoma and aid in diagnosis. White or hypopigmented lesions or those with pebbling, skin thickening, or thinning may represent skin conditions where biopsy is particularly useful for diagnosis and directing treatment.

- *Dermatitis*is a common finding, reportedly occurring in half of patients complaining of chronic vulvar complaints of an "itchy rash." It is often called contact dermatitis as it is often due to vulvar irritants including chronic vaginal discharge, semen, spermicides, soaps, propylene glycol found in many medicines, and allergic reactions. A comprehensive interview regarding hygiene practices, the presence of chronic vaginal discharge, and vulvar product use is very important. The skin lesions are sometimes poorly demarcated, erythematous, scaly, cracked and lichenified, thin "cigarette-paper" skin often with gray or white color. **Chronic cases may benefit from a biopsy**. Avoiding chronic "wetness" in the vulva and discontinuing any contributing irritants are important counseling point. The use of protective emollient, topical antibiotics [A&D ointment], and topical steroids is a treatment option (Schlosser 2010).
  - Acute or chronic vulvovaginitis candidiasis is associated with vulvar burning and

itching, erythema and edema of the vulva including the labia and vestibule, patches of thrush, and thick curd-like vaginal discharge.
    - Chronic conditions may show lichenification of the vulva and may be associated with pain and dyspareunia (Krapf 2016). Treatment with local or systemic antifungal products plus local drying hygiene techniques is indicated. Additional treatment for concomitant bacterial infection may need to be added if clinically indicated.
  - Atrophic vaginitis often plays a role in this condition and it may positively respond to local or systemic estrogen therapy. Normal vaginal epithelial and cervical discharge is an alkaline transudate with a pH ranging from 3.8 to 4.5. *Lactobacillus* produces acetic acid and helps to maintain a low vaginal pH. Lack of estrogen results in a higher vaginal pH and resultant change in vaginal flora.
- *Lichen sclerosus* is a chronic skin condition whose definite cause is not currently known. Lichen sclerosus is strongly associated with low endogenous estrogen levels, autoimmune diseases, and genetic factors (Higgins and Cruickshank 2012). Estimates are that between 1 in 70 and 1 in 1000 women have vulvar lichen sclerosus, a rate that is tenfold higher than men. On examination, typical lesions are shiny, flat, blanched white plaques with "crinkled tissue paper" affecting the vulva. There can be associated narrowing of the introitus, thinning, fusion of labia, phimosis of the clitoral hood, and fissures surrounded by purple or red borders (Eva 2012). A biopsy is recommended to confirm the diagnosis and rule out cancer. First-line treatment is high-dose topical steroid, clobetasol propionate, nightly for 4 weeks, then every other night for 4 weeks, and then twice weekly for maintenance (Chi et al. 2012; Thorstensen and Birenbaum 2012). Fissures, ecchymoses, hyperkeratosis, and erosions are expected to heal, but pigmentation changes may remain (Thorstensen and Birenbaum 2012). Avoiding chronic vulvar moisture is an important counseling point. The use of protective emollients, topical antibiotics, A&D ointment, and other topical hormones or steroids is optional treatment. Follow-up is critically important.
- *Vulvar HPV lesions and VIN.* There are at least 35 HPV subtypes that infect the anogenital tract. HPV infections in the vulva often appear as bumps or growths. They can be asymptomatic or cause itching, burning, bleeding, or pain. They can range in appearance from flat-topped papules, keratotic warts, or dome-shaped, flesh-colored papules to the true condylomata acuminate, cauliflower-like appearance (Boardman and Cooper 2007). Differentiating genital warts from a vulvar neoplasia from appearance alone can be difficult. **Generally, indurated, fixed, hyperpigmented, or ulcerative lesions or lesions that do not respond to treatment should be biopsied**. VIN can be white, red, dark, eroded, or raised. If the biopsy returns VIN, the patient should receive colposcopy and/or referral to gynecologic oncology (Boardman and Cooper 2007).
- *Paget's disease of the vulva* is a rare type of skin disease that is most often found in postmenopausal women. The most common complaint is itching or pruritus. It is very slow in spreading, but in some cases an invasive cancer of the vulva is found below the affected area (Shaco-Levy et al. 2010). The appearance of Paget's disease is sharply demarcated patches of red and white scaly skin, similar to the appearance of eczema. Biopsy confirms the diagnosis and rule out the underlying risk of cancer. Referral to gynecologic oncology is recommended as wide resection and further evaluations are the mainstay of treatment (Edey et al. 2013).
- *Squamous cell carcinomas* are the most common vulvar malignancy, but other pathologies include basal cell, melanoma, Bartholin's gland cancer, and non-squamous cell malignancy. These lesions present as a nodule or exophytic mass, asymptomatic lump, or flat or raised lesion with ulceration or excoriation. Melanomas are usually brown to bluish black,

but they may be nonpigmented. Lesions with these findings or any lesion that the patient reports have changed in size and shape should be biopsied.
- *An acrochordon* or skin tag may first present as a tiny soft bump on the skin. With time it may grow into a flesh-colored or darker lesion that is attached to the skin below often on a small stalk. A skin tag is generally painless but it can become irritated if rubbed or moved often. Biopsy is not necessary unless there are suspicious features or symptoms.

4.2 Biopsy Techniques

The Threshold for Performing a Vulvar Biopsy Should Be Low Chronic, recently changing, or exophytic lesions require a biopsy. Other indications are listed below. Techniques for three types of vulvar biopsies are detailed in Table 7.

Indications
Indications for performing a vulvar biopsy include the following:

- Possible malignancy
- Chronic, changing, or exophytic lesion
- Visible lesion and no definitive diagnosis
- Visible lesion, particularly white lesion not responding to usual therapy
- Lesions with atypical vascular patterns
- Benign-appearing lesions requiring definitive diagnosis

Contraindications
There are no absolute contraindications for vulvar biopsy. Relative contraindications include:

- Gross infection at site
- Coagulopathy, liver disease, anticoagulation medication use
- Allergy to local anesthetic
- Avoid biopsies on the clitoris or urethra

Approach Considerations
- Small, superficial lesions can be biopsied/removed using a shave biopsy. A shave biopsy samples the epidermis, and it may or may not include a section of the underlying dermis. Therefore, a shave biopsy may not provide information of the subcutaneous tissue. The lesion can be covered with a bandage.
- Punch biopsies can be used when the lesion is small enough for complete excision. Punch biopsies from 2 to 10 mm are available. Commonly punch biopsies from 3 to 5 mm are used.
- Large lesions, suspected inflammatory lesions, lesion suspicious for neoplasia, and ulcerated or pigmented lesions are often sampled using a punch biopsy. The punch biopsy can be used to either remove the entire specimen or take a small biopsy for diagnosis. In the latter case, the biopsy should include the edges of the lesion to get the best tissue for definitive diagnosis. Multiple punch biopsies may be necessary for larger lesion where areas appear to be different. Each biopsy should be placed in a separate container and labeled correctly.
- Larger lesions where complete excision with clear margins is desired may need excisional biopsy with suture repair.

Dressing
- The vulva is a difficult area to keep a dressing in place. Most vulvar biopsies are not covered with a dressing although a spot bandage can be used. Generally, a pad or panty liner is adequate.

Aftercare
- The patient should attempt to keep the area clean and dry, particularly after bowel movements as the biopsy site may be potentially contaminated with stool. If bleeding occurs, it can generally be stopped by direct pressure from the patient.
- 24 hours after biopsy with suture placements, showers are permitted, but hot tub baths should be avoided until healing is complete [usually about 5 days]. Area should be kept clean and dry and washed once to twice daily.

Table 7 Techniques for three types of vulvar biopsies

General: for all three techniques	Punch biopsy	Local resection	Shave biopsy
Consent patient and discuss risks and benefits. Risks may include infection, bleeding, inadequate sample, scarring, allergic reaction			
Eye protection should be used. Sterile gloves may be used			
Clean area with Betadine or equivalent; sterile drapes can be used			
Topical anesthetic agent may be applied prior to injecting a standard local anesthetic agent			
Using a large needle, 1–5 mL of 1–2% local anesthetic, such as lidocaine [preferably with epi]. The skin injection is done using a small needle (e.g., 25–30 gauge) to minimize pain (Eddowes 1990)			
After inserting the needle, the plunger is withdrawn to minimize risk of injecting into a vessel			
The anesthetic agent is slowly injected into the base and underneath the lesion, injecting enough to create a wheal			
	In general, the smallest punch biopsy [3 mm] that will adequately sample the lesion is used. For larger lesions, 4–5 mm biopsies are used. Multiple biopsies can be used	Larger lesions may need excisional biopsy with scalpel [i.e., 15 blade]	Elevate the lesion with a forceps, and then using either a scalpel, i.e., 15 blade, or curved scissors, use a single sweeping stroke to remove the lesion [or cut lesion with scissors with curved tips pointed upward]
	Punch biopsy is firmly placed against the skin, encompassing the entire lesion when possible and then rotated with a constant firm pressure both clockwise and counterclockwise until penetration through the skin to the base of the lesion. There is a change in tension as the punch	The lesion is grasped with forceps for stabilization or elevation. The scalpel is used to cut entirely around the lesion, generally including a margin around the entire lesion including the base. The incision is extended down to the base of the lesion. The specimen is held firmly with the forceps and	

(*continued*)

Table 7 (continued)

General: for all three techniques	Punch biopsy	Local resection	Shave biopsy
	biopsy enters the subcutaneous layer	removed using either the scalpel or Iris scissors	
	The punch is removed and the specimen grasped using forceps. [Curved Iris] scissors are used to cut the base of the biopsied tissue		
	Punch biopsies generally heal without suturing, but sutures may be considered for hemostasis	Suture closure is often used. A needle driver and suture, such as 4–0 monofilament or polyglactin, are used. Re-approximation of skin edges and lower tissue planes with one or more through and through stitches	Achieve hemostasis by pressure [or Monsel's solution]
	Monsel's solution or silver nitrate can be used [both may cause increased skin pigmentation and silver nitrate may cause scarring (Boardman and Cooper 2007)	Monsel's solution or silver nitrate can be used [both may cause increased skin pigmentation and silver nitrate may cause scarring (Boardman and Cooper 2007)	
Specimen is placed in pathology container [10% formalin]. For multiple biopsies, label each container accurately			

- Patients with suture placement are usually scheduled for suture removal about 7 days after the procedure if delayed absorbable suture is not used.

5 Conclusions

In-office gynecologic procedures are common office procedures that are now a mainstay of women's healthcare. Endometrial, cervical, and vulvar biopsies can be safely done in the office, and they allow the woman to quickly resume her normal activities. Many of these biopsies are done primarily to exclude the diagnosis of cancer, but additionally they are often helpful in establishing the correct diagnosis and treatment options.

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Treatment of Gynecological Congenital Anomalies

Irene Woo

Contents

Abstract

Congenital anomalies of the female reproductive tract results from defects in the embryologic development during organogenesis, fusion, or septum resorption. The American Society of Reproductive Medicine classifies congenital anomalies into seven categories, each with different reproductive outcomes and management options. This chapter will review the embryologic development of the Müllerian system, the different classification categories, useful imaging modalities and genetic attributes along with presentation and management of congenital anomalies of the female reproductive tract.

Keywords

Müllerian anomalies • Embryology • Infertility • OHVIRA

1 Introduction

The incidence of congenital Müllerian anomalies is approximately 4%. Infertile patients tend to have a higher incidence of these anomalies. In one study, infertile patients had a significantly higher incidence of Müllerian anomalies 6.3% compared to a fertile population 3.8% (Raga et al. 1997). The incidence can be as high as 15% in women with recurrent miscarriages (Acien 1993). While uterine Müllerian anomalies are the most common of the congenital anomalies

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of the reproductive tract with septate and arcuate uteri accounting for over half of the malformations, other complex malformations involving the mesonephric system occur at a much lower rate (Speroff and Fritz 2011). These Müllerian anomalies associated with extragenital malformations may have a genetic origin or may be due to a teratogenic exposure such as diethylstilbestrol (DES). In most common Müllerian anomalies, however, there is no identifiable genetic mutation, and it is likely that these malformations are a result of polygenic and familial mechanisms.

To further complicate the diagnosis of congenital malformation of the female genital tract, there are currently four different classification systems. These include the American Fertility Society (AFS) now American Society of Reproductive Medicine system; the embryological–clinical classification system of genitourinary malformations; the Vagina, Cervix, Uterus, Adnexa and associated Malformations (VCUAM) system; and the newest European Society of Human Reproduction and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) classification system. None of these have proven to be completely comprehensive of all the multitude of different congenital anomalies seen in the female reproductive tract. The newest classification system, ESHRE/ESGE classification, does incorporate more of the complex vagina, cervix, uterus, and adnex-associated malformations (Acien and Acien 2015). While each system has limitation, the ASRM classification system has been widely adopted as the main classification system due to its simplicity and ease of use. This chapter will mainly focus on the ASRM classification and add discussions of some of the anomalies, particularly obstructive anomalies that are not adequately represented with this classification system (Di Spiezio Sardo et al. 2015).

Müllerian anomalies mainly originate from failure in three different stages of embryologic development: failure in organogenesis, fusion, or septum resorption or a combination of these. When there is a defect in organogenesis of either one of the Müllerian ducts, this may lead to failure of development of part of the uterus or of the entire uterus resulting in uterine agenesis, or unicornuate uterus. Failure of the two Müllerian ducts to fuse in the midline may result in a uterine didelphys or bicornuate uterus. Thirdly, normal embryologic development of the uterus and vaginal canal requires the resorption of the central septum. Defects in resorption of the septum can result in a persistent uterine or vaginal septum.

Müllerian anomalies are important not only for their effect on fertility but for their association with the renal system and for certain obstructive malformations that may cause severe clinical symptoms. This chapter will review the embryologic development of the Müllerian system, a brief examination of genetic attributes, and the different classifications, presentation, and management of Müllerian anomalies.

2 Embryology

At the fifth week of gestation, the urogenital ridge is formed along the posterior coelomic wall. The pronephros is located laterally and is eventually replaced by the mesonephros (also known as Wolffian duct). The distal Wolffian duct forms the uteric bud that grows cephalad to induce the development of the kidney (metanephric system). Failure of a Wolffian duct to form will therefore affect formation of the ipsilateral kidney and ureteral system.

By the sixth week of gestation, the paired paramesonephric (Müllerian) ducts grow caudally alongside the Wolffian ducts as their guide. Failed formation of the Wolffian ducts may also lead to defects in formation of the ipsilateral Müllerian structures. The growth of Müllerian structures is initially guided by the presence or absence of the SRY, the sex-determining gene. The SRY gene is found on the Y chromosome and starts the process that causes a fetus to develop male gonads[testes]. In the absence of the SRY gene and the presence of an incompletely identified female-determining factor, the female anatomy results.

During this time, the cloaca [the posterior orifice that becomes the opening for the urinary, digestive, and reproductive tracts] is divided by

the urorectal septum. The posterior portion develops into the anorectal canal while the anterior portion becomes the urogenital sinus. The urogenital sinus connects and fuses to the Müllerian ducts[the two ducts have already fused together] and ultimately develops into the bladder, lower two-thirds of the vagina, and the hymen. Transverse vaginal septums may result if there is a defect in the connection or fusion of Müllerian ducts to the urogenital sinus.

By the tenth week of gestation, the two paramesonephric (Müllerian) ducts have fused in the midline, and the fusion extends caudally and cephalad to produce the primordial uterus and upper one-third of the vagina. In females, the absence of testes and its products AMH and testosterone permits the development of Müllerian structures and regression of Wolffian ducts by 12 weeks of gestation. Vestiges of Wolffian ducts include parovarian and Gartner duct cysts. The thin septum remaining between the two cavities after fusion is eventually resorbed between 14 and 18 weeks of gestation in the cephalad direction yielding a single cavity of uterus and the lumen for the upper one-third of the vagina.

By the 22nd week of gestation, the uterus has taken on the structure of the adult organ. By week 32, glandular secretory activity is present, caused by placentally derived steroid hormones. After delivery, with the fall in steroid hormones, the endometrium regresses to an atrophic state (Fig. 1).

3 Molecular Origin

The embryonic events described above are driven largely by the expression of secreted ligands of the wingless-type MMTV integration site (Wnt) family (Wnt4, Wnta, Wnt7a) and transcriptional regulators of the homeobox HOX gene family (Strauss JF 2014). Müllerian ducts are absent in female mice lacking Wnt4 (gene expressed in the mesenchyme). In women, Wnt4 null mutations are associated with Müllerian duct regression and a phenotype including hyperandrogenemia. WNT9b is expressed in the Wolffian duct epithelium and is necessary for Müllerian duct extension (Carroll et al. 2005). WNT7a expression is found in the luminal epithelium of the Müllerian duct and involved in paracrine signaling to the endometrial mesenchyme and proper development of the uterus (Strauss JF 2014). In mice lacking WNTta, the oviduct is not clearly demarcated from the upper uterine horn and the uterus develops cellular characteristics that are similar to the vagina (including a stratified epithelium without uterine glands) (Miller et al. 1998; Timmreck et al. 2003). Postnatal expression of HOXA10 and HOXA11 in the uterus is also lost. However, women with Müllerian anomalies have not been associated with mutations in WNT7A.

The HOX (homeobox) genes encode a highly conserved family of transcription factors that play a critical role in mapping the body plan of an embryo. The HOX genes organize cells along the anterior–posterior axis and direct them to select a particular pathway of development. Mammalian HOX genes are arranged in four different clusters, designated A through D, with each cluster organized in a linear arrangement that parallels the order of expression along the anterior–posterior body axis (Strauss 2014). The expression of HOXA genes in the human and mouse reproductive tract is similar, with HOXA9 being expressed in the fallopian tubes, HOXA10 and HOXA11 in the uterus, HOXA11 in the cervix, and HOXA13 in the upper vagina (Ekici et al. 2013; Taylor et al. 1997). Mice with targeted deletions in the HOXA10 and HOXA11 genes have subtle abnormalities in uterine morphology, reduced endometrial stromal development, and reduced expression of leukemia inhibitory factor (LIF). Likely HOXA10 and HOXA11 are involved in endometrial receptivity and the implantation process (Xu et al. 2014).

4 Classification for Müllerian Anomalies

As discussed above, many clinical classifications have been developed to improve and standardize the definition of the numerous variants in Müllerian anomalies. One of the most broadly used classification systems is introduced by the

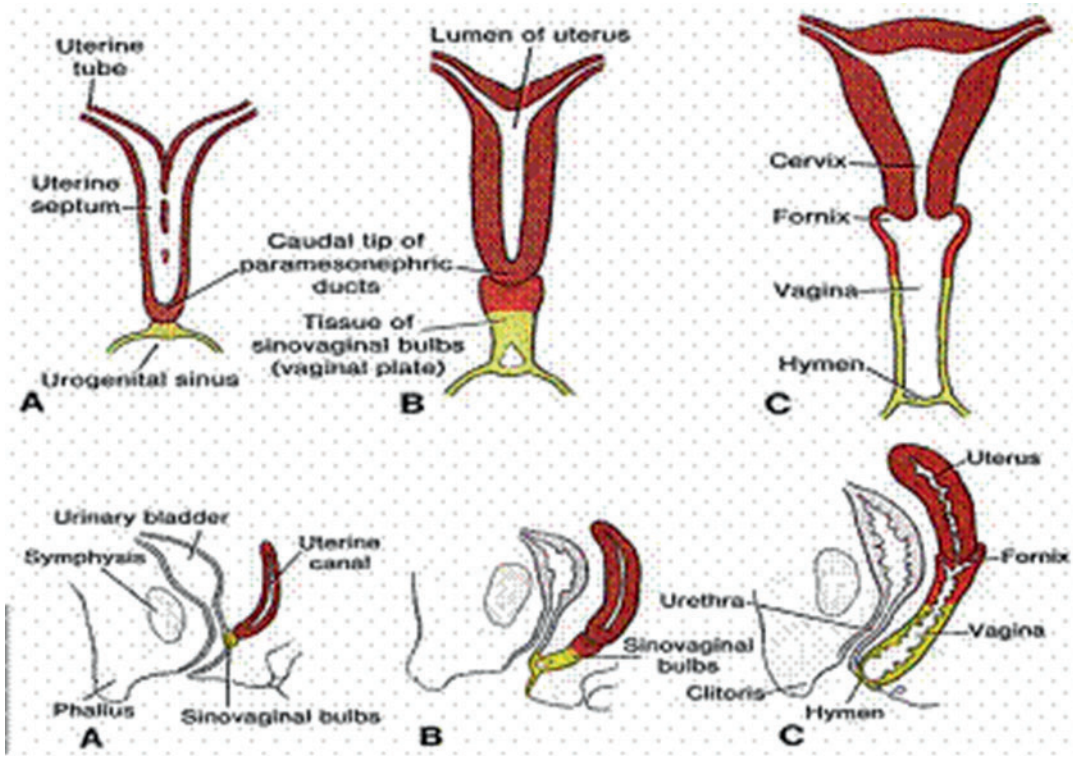

Fig. 1 Complete formation of the genital tract

American Fertility Society/American Society of Reproductive Medicine (AFS/ASRM) in 1988. The ASRM classification consists of seven categories according to Müllerian development: (1) hypoplasia/agenesis, (2) unicornuate, (3) didelphys, (4) bicornuate, (5) septate, (6) arcuate, and (7) DES drug related. The ASRM classification is presented in more detail below.

The first category is uterine agenesis/hypoplasia. Failure of the development of Müllerian ducts result in various degrees of agenesis or hypoplasia of the uterus, cervix, and upper two-thirds of the vagina. Müllerian agenesis is the second most common cause of primary amenorrhea, with the first being gonadal dysgenesis. With Müllerian agenesis, there are normal gonads and patients develop normal secondary sexual characteristics. This category includes varying degrees of agenesis or hypoplasia of the vagina, cervix, fundus, and fallopian tubes. The most common subtype is Mayer–Rokitansky–Kuster–Hauser syndrome. The incidence is approximately 1 in 4,500 women. There are two main types of MRKH. Type 1 MRKH is mostly isolated Müllerian hypoplasia (consisting of a combined agenesis of the uterus, cervix, and upper part of the vagina). In Type 2 MRKH, also known as Müllerian Renal Cervico-thoracic Somite (MURCS association), in addition to the Müllerian agenesis, there is involvement of the renal system including unilateral agenesis, ectopic kidneys or horseshoe kidneys, skeletal anomalies including fused vertebrae (often cervical) and scoliosis, hearing defects, and occasionally cardiac and digital anomalies.

Class II consists of the unicornuate uterus. Four possible subtypes can develop: (i) absent rudimentary horn, (ii) rudimentary horn without endometrium, (iii) communicating rudimentary horn with functional endometrium, and (iv) noncommunicating rudimentary horn with functional endometrium. The last subtype may lead to significant obstructive clinical symptoms. Patients may present with pelvic mass, cyclic pelvic pain, and postmenstrual dysmenorrhea

due to the obstructed flow from the non-communicating horn. Due to the close embryological development, renal anomalies are reported in roughly 40% of unicornuate patients that are ipsilateral to the rudimentary horn. A majority (67%) of renal involvement present as renal agenesis. Other anomalies include ectopic kidney, horseshoe kidney, renal dysplasia, and duplicated collecting systems (Speroff and Fritz 2011).

The next two classes result from a defect in fusion of the Müllerian ducts.

Class III, uterine didelphys is the result of complete non-fusion of the uterus, cervix, and upper vagina. The individual uterine horns are fully developed and approximately normal in size. A deep fundal cleft and two cervices are present. A longitudinal or transverse vaginal septum is commonly present. A common complex uterine anomaly, not specifically addressed in ASRM classification is the Obstructed HemiVagina with Ipsilateral Renal Agenesis (OHVIRA) syndrome also referred to as the Herlyn–Werner–Wunderlich syndrome which will be discussed later in the chapter (Mandava et al. 2012).

Class IV is a bicornuate uterus. This is the result of partial non-fusion of the Müllerian ducts. There is central myometrium that may extend to the level of the internal cervical os (bicornuate unicollis) or external os (bicornuate bicollis), with a fundal cleft >1 cm deep. The horns of the bicornuate uteri are not as fully developed and are smaller than those in the didelphys uteri. On hysterosalpingogram (HSG) there is often a widened (>4 cm) intercornual distance (a straight line measured from one ostium to the other) and a widened ($>60°$) intercornual angle that is used to differentiate a bicornuate uterus from the class V septate uterus (Syed 2013).

Class V and VI are defects of resorption of the septum between the fused Müllerian ducts. Class V includes uterine septums that are partial or complete (the septum extends to the internal cervical os). Septums are usually composed of avascular fibrous tissue but may also contain myometrium. In comparison to a bicornuate uterus on HSG, the intercornual distance in a septate uterus is usually <4 cm. The differentiation between a septate and bicornuate uterus is important because they differ in their reproductive prognosis and treatment. The morphology of the outer fundal contour may be critical in making the correct diagnosis. The uterine fundus in septate uterus may be convex, flat, or slightly concave (<1 cm fundal cleft). One formula proposed is using a 3D ultrasound and tracing a line to join both tubal ostia. If this line crossed the fundus or was ≤ 5 mm from the apex of the fundus, the uterus was considered bicornuate, whereas if the apex was >5 mm from the fundus, the uterus was considered septate (Bermejo et al. 2010; Troiano and McCarthy 2004).

Arcuate uterus, class VI, involves a mild indentation of the endometrium at the uterine fundus. ASRM classification defines the internal indentation as ≥ 1 cm and <1.5 cm deep to differentiate the arcuate configuration from the septate. However, this class in general is highly controversial, and it remains unclear whether this variant should be classified as a true anomaly or as an anatomic variant of normal. Data regarding the reproductive outcome of patients in this category generally indicate that an arcuate uterus is compatible with normal pregnancy and delivery.

The last category, class VII, is diethylstilbestrol-related anomaly. The uterus is typically hypoplastic with a T-shaped uterine cavity. There may also be abnormal transverse ridges, hoods, and stenosis of the cervix. Several million women were treated with diethylstilbestrol (DES) to prevent miscarriage between 1945 and 1970. The drug was promptly withdrawn from use in pregnant women when it was found that up to 15% of newborn girls who were exposed to DES had uterine malformations and an increased risk of vaginal clear cell carcinoma (Speroff and Fritz 2011) (Fig. 2).

5 Imaging Modalities

Accurate diagnosis of congenital anomalies of the reproductive tract is still clinically challenging, as there are no clear definitions or objective diagnostic criteria even in the widely accepted standard ASRM classification system. The currently available diagnostic methods are discussed below.

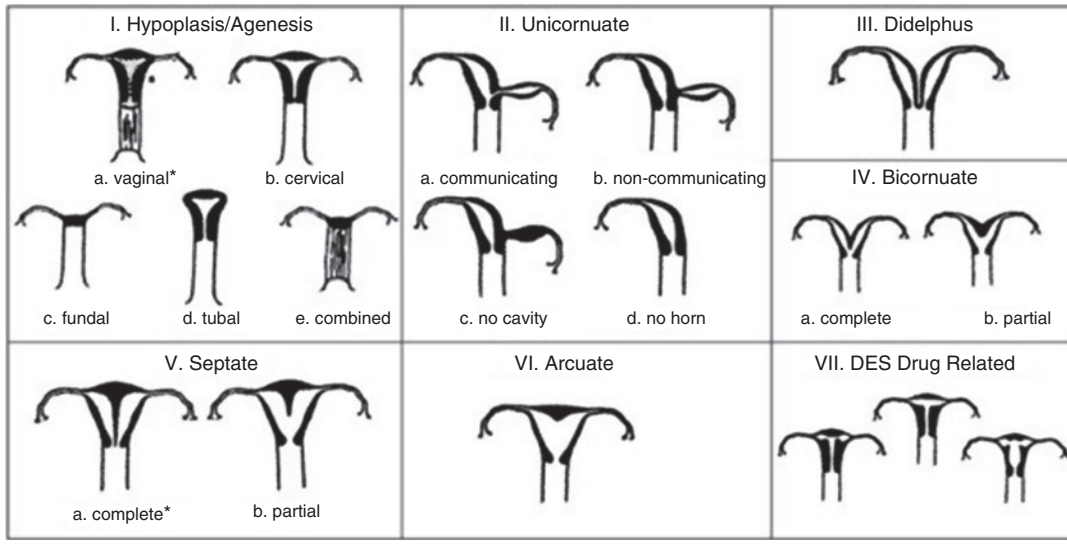

Fig. 2 American Fertility Society Classification for Müllerian anomalies

First, the most important aspect of clinical evaluation is the history and physical exam. Clinical presentation of amenorrhea at puberty or refractory dysmenorrhea shortly after menarche should alert the physician to possible congenital anomalies of the reproductive tract. A thorough inspection and pelvic exam may reveal the vaginal and cervical malformations including aplasia, double cervices, and longitudinal septum.

Hysterosalpingography (HSG) is a great modality to evaluate the intracavitary pathology and tubal patency in infertile patients; however, for Müllerian anomalies, it is much less reliable. HSGs are unable to provide information regarding the thickness of the uterine wall or external contour of the uterus. Neither will it provide information on noncommunicating rudimentary horns.

Two-dimensional ultrasonography is a quick, low-cost, and noninvasive test that can provide reliable measurements for the cervix, uterine cavity, uterine wall, and external contour of the uterus. It is often the primary imaging test obtained for evaluation of pelvic anatomy. If the patient is virginal or unable to tolerate a vaginal ultrasound, translabial ultrasound can also provide useful information and can pick up abnormalities including hematocolpos or tubal/ovarian pathologies. Similarly, saline infusion sonography allows for all the benefits of an ultrasound in addition to evaluating the endometrial cavity for septum or polyps.

Currently 3D ultrasound can also be a diagnostic tool. The reconstructed 3D image allows evaluation of the coronal plane of the uterus. However, this methodology requires special equipment and more advanced technician.

Magnetic resonance imaging provides highly reliable information of all the pelvic structures and additionally has the ability to evaluate the renal system. Complex and obstructing anomalies can be accurately appreciated.

In a systematic review, 3D US had the highest degree of overall diagnostic accuracy (97.6%), while MRI was shown to correctly subclassify 85.8% of anomalies (Grimbizis et al. 2001). Diagnostic accuracy for the other modalities: saline infusion sonogram (96.5%), 2D US (86.6%), and HSG (86.9%).

The gold standard for diagnosis of Müllerian anomalies still remains a combination of laparoscopy and hysteroscopy. Endoscopy provides direct visualization of the vagina, cervical canal, uterine cavity, and uterine fundus. However, it is more invasive and should be reserved in the context of concomitant therapeutic surgery.

6 Reproductive Outcomes and Management Options

Women with uterine anomalies have poorer reproductive outcomes and lower pregnancy rates compared with women with normal uteri. This same trend is noted in spontaneous and ART-conceived pregnancies (Lin 2004). Women with Müllerian anomalies have higher rates of preterm delivery, preterm premature rupture of membranes, small for gestational age infants, higher rates of malpresentation, and subsequent higher rates of cesarean delivery (Hiersch et al. 2015).

Management of patients with Müllerian agenesis includes a multidisciplinary approach with psychosocial counseling and emphasis on the possibility of healthy sexual relationships in the future. Patients should also be counseled regarding options of assisted reproductive techniques and use of gestational surrogate. Once patients are emotionally ready and express desire for correction, nonsurgical creation of the vagina is the appropriate first-line treatment. Patients are advised to self-dilate with successive dilators on the vaginal dimple for 30 min to 2 h a day. Another technique utilizes a bicycle seat stool to provide perineal pressure. Although it may require several months, self-dilation has been shown to be successful in creating a functional neovagina in 90–95% of women (ACOG 2013).

Surgical creation of a neovagina is an alternative option. The most common procedure is the modified Abbe–McIndoe, in which a space is dissected between the rectum and bladder and a split-thickness skin graft mold is placed. Patients must then use vaginal dilators consistently postoperatively. Other less common procedures for surgical creation of neovagina include Vecchietti procedure, mobilization of peritoneum, and bowel graft neovagina.

In one review, unicornuate uterus had the poorest overall reproductive outcome, with the highest frequency of preterm deliveries and lowest live birth rates (Heinonen et al. 1982). It has been theorized that the decreased muscle mass and abnormal uterine vasculature contribute to the significantly poorer reproductive outcomes (Lin 2004). Except for cervical cerclage in appropriate cases, unicornuate uterus often does not warrant surgery; however, in specific cases particularly when the rudimentary horn has functional endometrial tissue, the rudimentary horn should be removed. As described above, the functional endometrium may cause cyclic pain and hematocolpos. Pregnancy may also occur in the embryological remnant resulting in uterine rupture (Holden and Hart 1983). Ectopic rates are also elevated in unicornuate uterus at 4.3%, twice as likely than baseline population (Heinonen et al. 1982).

Uterine didelphys, when associated with an obstructed hemivagina (OHVIRA) syndrome, does require surgical correction. When it is patent uterine didelphys, pregnancy outcomes are generally good, although some studies have noted higher rates of miscarriage and premature labor when compared to the general population. Some patients have no reproductive difficulties, theoretically because uterine didelphys is the complete duplication of a single uterus (Grimbizis et al. 2001; Raga et al. 1997).

Bicornuate uterus is a relatively common anomaly. Live birth rates are near normal with some studies noting higher rates of preterm birth and malpresentation (Acien 1993). Value of metroplasty is unclear. There is limited data showing improvement in obstetric outcomes after surgical reconstruction for bicornuate uterus and is not generally recommended. However, surgery may be considered in some patients, particularly in patients with recurrent miscarriages or poor obstetrical outcome, but treatment should be individualized (Maneschi et al. 1993; Speroff and Fritz 2011). If surgical correction is performed, the techniques available include Strassmann unification of uterine horns, Tompkins fundal bivalve metroplasty, and Jones wedge metroplasty (Strassmann 1966). There are also reports of higher incidence of cervical insufficiency in patients with bicornuate uterus. While routine prophylactic cerclage are supported by some studies (Golan et al. 1990; Yassaee and Mostafaee 2011), a more conservative approach would be to obtain serial ultrasound examinations starting

between 16 and 20 weeks of gestation for cervical length and cerclage placement when clinically indicated (Chifan et al. 2012).

The septate uterus has been associated with the highest rate of miscarriage in comparison to the other Müllerian anomalies, with miscarriage rates up to 75% in one series (Lin 2004). The mechanism is unclear but often believed to be implantation into the poorly vascularize fibrous septum which may lead to disruption in implantation. Other adverse pregnancy outcomes include premature delivery, abnormal presentation, and intrauterine growth restriction. In one study women undergoing hysteroscopic resection of a uterine septum demonstrated a significant decrease in miscarriage rates from 80% to 17% and an increase in the live birth rates from 18% to 91% (Freud et al. 2015). In addition to poor obstetrical outcomes, septums may also be associated with infertility. After septum resection in infertile patients, the time needed to achieve pregnancy was significantly shorter than controls (Gergolet et al. 2012). With the abundant evidence in the literature, septate uterus should be repaired in women with adverse pregnancy outcome or with unexplained infertility.

Prior to surgery, it is helpful to distinguish a fibrous septum from a muscular septum. Evaluation with an MRI for this reason may be valuable. A fibrous septum can be more easily repaired by a hysteroscopic approach. Incision with hysteroscopic scissors usually causes the fibrous septum to retract, so an excision is not necessary. A residual septum <1 cm from the serosal surface does not need to be resected as it is not associated with the poor obstetrical outcomes (Fedele et al. 1996). Simultaneous laparoscopy during hysteroscopic resection is necessary to both confirm fundal contour and guide extent of dissection. Thicker muscular septums may require a more extensive surgery with metroplasty. After resection of a septum, some experts recommend 2.5 mg conjugated estrogen for 25 days and adding 10 mg medroxyprogesterone acetate for the last 10 days to help prevent adhesions and intrauterine scarring though the data is limited.

An arcuate uterus appears to have no impact on obstetric outcome. Live birth rates are similar to women without Müllerian anomalies, and therefore there is no additional management needed for women with arcuate uterus.

7 Non-ASRM Classifications

Cervical and vaginal anomalies are subcategories that are often poorly described and unclassified in the ASRM system. Defects include imperforate hymen, transverse vaginal septums, cervical dysgenesis and cervicovaginal agenesis, obstructed hemivagina including OHVIRA, and lower vaginal atresia. These congenital anomalies often lead to obstruction of menstrual flow. Patients often present at puberty with primary amenorrhea or progressively worsening episodes of abdominal pain shortly after menarche.

Imperforate hymen is the most common outflow tract obstruction, with incidence as high as 1/2,000 (Dietrich et al. 2014). Visual inspection of the vulva often shows an intact hymenal membrane that is bulging or bluish. Diagnosis can be confirmed with a rectal exam palpating for the vaginal bulge, or with abdominal or translabial ultrasound.

Presentation of the transverse vaginal septum is very similar to the imperforate hymen, though these are much rarer (1/2,100–1/72,000). The septum can be anywhere along the length of the vagina but are often in the upper one-third. The hymenal ring appears normal. Insertion of a Q-tip or gloved finger into the vaginal canal can assess the vaginal depth.

Complete or partial vaginal atresia may also result in obstruction of menstrual flow as the uterus and cervix are normally functioning. The hymen ring will appear normal, but the vagina appears nonpatent. In contrast to imperforate hymen, there is no bulge present at the perineum, but there may be a palpable abdominal mass. Cervical dysgenesis is a rare disorder, and diagnosis will likely require a combination of physical inspection and imaging modalities.

The most common partially obstructed Müllerian tract anomaly is the OHVIRA syndrome. These patients often present a few years after menarche as they do have menstrual flow

that collects over time. Progressive refractory dysmenorrhea and increasing size of an abdominal mass (hematocolpos) often compels patients to present to the emergency department for evaluation. An obstructed uterine horn with functional endometrium can present in a similar fashion with worsening dysmenorrhea after the onset of menarche. An MRI is helpful to identify any connection between the obstructed horn and the nonobstructed uterine cavity.

Along with significant clinical symptoms, all of these obstructions have been associated with higher rate of endometriosis, hematosalpinx, and pelvic inflammatory disease. While medical suppression with combined oral contraceptives, or gonadotropin agonist are options, they are often insufficient for pain control. Surgical therapies are reviewed below for the different anomalies.

It is important to differentiate an imperforate hymen from vaginal agenesis, because the surgical management of imperforate hymen is very simple. It involves creating a cruciate or circular excision of the hymenal bulge. Suction of the hematocolpos essentially resolves pain and results in a patent vaginal canal. In cases of lower vagina atresia, a much more complex surgery with a highly skilled surgeon is required. One surgical method is to dissect the rectovaginal and vesicovaginal spaces in order to expose the normal vaginal mucosa. This mucosa is then "pulled through" and sutured to the perineum.

Transverse vaginal septums also require more skill than a stab incision to open. The septum should be carefully excised, and the vaginal mucosa of the upper and lower part of the vagina is reanastomosed with interrupted stitches to create the full length of the vaginal canal. Postoperatively the patient must continue with manual dilation to prevent stenosis.

In OHVIRA, the first step is to identify the normal cervix. The septum can then be excised, and the vaginal mucosa of the obstructed side is circumferentially anastomosed to the fully developed side. Care must be paid not to injure the cervix on the obstructed side during septum resection and decompression.

8 Conclusion

In summary, congenital anomalies of the female reproductive tract may present in many different ways depending on the stage of embryological development that is affected. Clinicians should remember to keep Müllerian anomalies in the differential when pubertal girls present with primary amenorrhea or when young women present with refractive dysmenorrhea and pelvic mass. While diagnosis and classification remain challenging, the ASRM classification is the simplest and most user-friendly method. Clinicians should incorporate a multidisciplinary team approach in discussion regarding management options and future fertility desires. Treatment should be individualized to the goal of the patient.

9 Cross-References

- ▶ Abnormal Vaginal Bleeding During the Early Reproductive Years
- ▶ Anatomy of the Female Genital System

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Management of Adnexal Masses

Donna Shoupe

Contents

Abstract

The differential diagnoses of an adnexal mass range from benign functional ovarian cysts to metastatic ovarian carcinoma. The goal of the clinician is to differentiate benign conditions from more serious life-threatening or malignant conditions. Work-up of an adnexal mass demands a thorough history and physical exam followed by gray-scale transvaginal ultrasonography (Givens et al. Am Fam Physician 2009;80(8):815–20). Findings that are suspicious for carcinoma include symptoms of bloating, increasing pelvic or abdominal pain, weight loss coupled with the presence of a solid component or complex mass, positive Doppler flow in the mass, thick septations, mural nodules, or presence of ascites. In an asymptomatic postmenarchial woman, [regardless of age] with an adnexal mass, transvaginal ultrasonography is the initial imaging study of choice (Guideline Summary. American College of Obstetricians and Gynecologists NGC.006539 2007 Jul reaffirmed 2011. https://www.guideline.gov/summaries/summary/12631. Assessed 2 Sept 2016). Simple ovarian "simple cysts" can be found routinely in both premenopausal and postmenopausal women (Healy et al. Menopause 2008;15 (6):1109–14), and hemorrhagic corpus luteum cysts (3–5 cm in size) can occur in early (within 5 years of) menopause (Seungdamrong

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Table 1 Differential diagnoses of an adnexal mass

Gynecologic benign ovarian	Paraovarian cysts	Gynecologic malignant ovarian/tubal	Tubal or retroperitoneal cancers
	Corpus luteum		Borderline tumor
	Follicular/functional cyst, simple cyst		Epithelial carcinoma [clear cell, serous, mucinous, endometrioid]
	Mature cystic teratoma [dermoid]		Ovarian sarcoma
	Ovarian torsion		Ovarian germ cell tumors
	Polycystic ovaries		Sex cord or stromal tumor
	Serous and mucinous cystadenoma, cystadenofibromas	Gynecologic malignant non-ovarian	Endometrial cancer
	Theca-lutein cyst/luteoma of pregnancy		Fallopian tube cancer
	Tubo-ovarian abscess	Nongynecologic benign	Appendiceal abscess/ appendicitis
	Endometrioma		Diverticular abscess
Gynecologic non-ovarian benign	Ectopic pregnancy		Pelvic kidney
	Leiomyoma		Bladder diverticulum
	Hydrosalpinx		Nerve sheath tumor
	Para-tubal cyst		Peritoneal inclusion cyst
	Endosalpingiosis		Ureteral or bladder diverticulum
	Mullerian/Wolffian duct remnants [paramesonephric cysts [cyst of Morgagni]]	Nongynecologic malignant	Gastrointestinal cancer/ Krukenberg
			Metastatic cancer [colon, breast, etc.]
			Retroperitoneal, intraligamentous cancer
			Omental cysts
			Malignant peritoneal mesothelioma

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Keywords

Adnexal mass • Endometrioma • Cystic teratoma • Dermoid • Ovarian cancer • Pelvic ultrasound • Simple cyst • Ectopic pregnancy • CA 125 • Tumor markers • Luteoma • Complex mass • Torsion • Functional cyst • Unilocular cyst • Septations • Solid mass • Papillary components • Color flow

1 Introduction

The adnexal mass is one of the most common gynecologic conditions. It is estimated that US women have a 5–10 % lifetime risk of undergoing surgery for a suspected adnexal mass (Nagell and Miler 2016). Adnexal masses may be suspected in both symptomatic and asymptomatic women. In premenopausal women, the most common adnexal masses include physiologic follicular cysts and corpus luteum, ectopic pregnancy, polycystic ovaries, endometrioma, benign neoplasm, or tubo-ovarian abscess. In postmenopausal women, common adnexal masses include fibroids and benign neoplasms (Table 1). The first

approach of the clinician is to establish that the condition does not mandate immediate intervention [ectopic pregnancy or torsion] and then to determine whether the adnexal mass is "almost certainly benign in nature," likely or definitely malignant, or indeterminate.

2 Presenting Symptoms

There is a large spectrum of symptoms that patients with an adnexal mass may have as presenting symptoms. Common presenting symptoms of an ectopic pregnancy include vaginal bleeding, unilateral pelvic pain, and a positive pregnancy test. A patient complaining of intermittent severe pain aggravated by movement that may be associated with nausea or vomiting suggests ovarian torsion. These are both conditions that need immediate attention as they need immediate intervention. Patients presenting with fever, purulent vaginal discharge, and cervical motion tenderness may have pelvic inflammatory disease or a tubo-ovarian abscess. An endometrioma/endometriosis may be suspected in patients with infertility and long-standing severe dysmenorrhea and dyspareunia. Premenarchal bleeding or postmenopausal bleeding with an adnexal mass may suggest a granulosa tumor. Midcycle pain may indicate ovulation or Mittelschmertz.

There are important factors in the history and nature of the presenting symptoms that are risk factors for ovarian cancer. These include age over 60, nulliparity, infertility, no use of oral contraceptives, family history of breast, colon or ovarian cancer, increased abdominal size, bloating, urinary urgency or frequency, difficulty eating, weight loss, back pain, lack of energy, and non-acute abdominal or pelvic pain (Goff et al. 2000; Olson et al. 2001).

3 History

The history includes the following:

- Identification and careful review of the patient's symptomatology includes an evaluation of pain [location, severity, character, timing, radiating, back pain], bleeding [amount, timing, lightheadedness], GI problems [eating problems, bloating, bowel function], bladder issues [frequency, dysuria, urgency], presence of vaginal discharge [color, quantity], fever or chills, aggravating or mitigating factors, and other associated complaints.
  - Symptoms associated with ovarian cancer are often vague in nature.
- Medication review [contraceptive history [IUD, OCPS, pain meds].
- Surgical review [tubal ligation, adnexal surgery, prior myomectomy].
- Medical problems review [history of endometriosis, fibroids, assess surgical risk].
- Obstetrical and gynecologic history [normal cycle length, pregnancy history, pain with intercourse, days and heaviness of menstrual flow, cramps, history of STIs, PID, new partner, prior Gyn diagnoses].
- Family history [breast, ovarian, or colon cancer, bleeding or clotting problems].
- Weight changes, changes in eating pattern, change in energy levels.

4 Physical Exam

Physical exam includes the following:

- Vital signs and general assessment [amount of distress, fast pulse rate, low blood pressure, fever, ease of movement]
- Abdominal exam per four quadrants [tenderness, guarding, bloating, distension, bowel sounds, rebound, ascites, inguinal lymph nodes, and when appropriate cervical, axillary, and supracervical lymph nodes]
- Pelvic exam
  - Careful visual exam of the vulva and vagina [discharge or bleeding, vulvar/vaginal/cervical mass, dilation, stricture, or discoloration]
  - Bimanual exam of the uterus [cervical motion tenderness, uterine size, shape, consistency, uterine tenderness, mobility, guarding, bladder tenderness, or pain]

- Careful adnexal evaluation [adnexal mass, size, shape, mobility, consistency, tenderness, guarding]
- Rectovaginal exam [masses, uterosacral nodularity]

5 Laboratory and Imaging Studies

- In reproductive aged women:
  - **Pregnancy test urine and CBC: if positive pregnancy test, then pelvic ultrasound and quantitative B-hCG are obtained:**
    - If B-hCG is over 2,000 mIU/ml, there is presence of an adnexal mass, and no gestational sac is seen intrauterine, an ectopic pregnancy is suspected.
      - CBC along with vital signs establishes presence of anemia/amount of blood loss and urgency of intervention.
    - Adnexal masses coincident with a viable intrauterine pregnancy have a low risk of malignancy and are generally asymptomatic. See below (American College Ob/Gyn 2007; Whitecar et al. 1999).
  - CBC
    - WBC elevated with shift: PID or tubo-ovarian abscess is suspected [cervical motion tenderness, yellow vaginal discharge, fever, GI symptoms].
      - Pelvic ultrasound establishes the presence or absence of adnexal masses and characteristics of the masses.
      - Gray-Scale transvaginal Imaging is the recommended imaging modality for evaluation of an adnexal mass (Mitchel et al. 2009).
      - Cervical cultures obtained for gonorrhea and chlamydia, STD screening.
    - If prolonged or acute heavy bleeding:
      - CBC, clotting studies [blood dyscrasias particularly important to rule out in young adolescent women with prolonged bleeding episodes.
      - Pelvic ultrasound may demonstrate uterine fibroids, adenomyosis.
      - Routine screening with CA-125 in a premenopausal woman with an adnexal mass (American College of Ob/Gyn 2007) or without an adnexal mass (US Preventive Service Task Force 2004) is **not recommended**.
      - Particular findings on pelvic ultrasound that are suspicious for cancer are discussed in imaging studies below and Table 3.
        - With suspicious findings for malignancy, follow-up studies with MRI or CT along with CA 125 and other biomarkers (see below under postmenopausal women) are used to further characterize the mass.

- In postmenopausal women:
  - Pelvic ultrasound is used to identify the nature of the adnexal mass [see below]. Follow-up CT or MRI may be indicated based on ultrasound and clinical findings.
  - CA-125 and other tumor markers are not used for screening in the absence of an adnexal mass.
    - CA-125 is elevated from a number of benign as well as malignant conditions (Table 2).
    - **CA-125 should be drawn in a postmenopausal woman with an adnexal mass to guide treatment** (Royal College of Ob/Gyn 2016). CA-125 is also followed postoperatively to monitor treatment response.
      - Any elevation in CA-125 in postmenopausal women needs further evaluation (Guidelines 2016).
      - Only 50 % of stage 1 cancers have elevated CA-125.
      - Ca-125 is elevated in 80 % of ovarian epithelial cancers.
  - If a granulosa cell tumor is suspected, inhibins A and B are drawn and followed postoperatively.
  - If a germ cell tumor is suspected, quantitative B-hCG and alpha-fetoprotein are drawn and followed postoperatively.
  - CEA may be elevated with mucinous cancer associated with the ovary or GI tract [also

Table 2 Causes of elevated CA-125

Benign conditions	Malignant conditions
Endometriosis/endometrioma	Ovarian cancer
Pelvic inflammatory disease	Breast cancer
Uterine fibroids	Endometrial cancer
Pleural, peritoneal fluid or disease: presence of fluid in cul-de-sac, pelvis, abdomen representing blood, fluid, or ascites	Lung cancer
Diseases involving serosal surface	Pancreatic cancer
Cirrhosis with or without ascites	

reported elevated in breast, pancreas, thyroid, and lung cancer] but can also be elevated with smoking, cholecystitis, cirrhosis, diverticulitis, or IBS.
- OVA1, approved by the FDA in 2009, is a test that included five biomarkers. The results of the biomarkers are used to generate an ovarian malignancy risk score.
- The Risk of Malignancy Algorithm (ROMA), approved by the FDA in 2001, combines HE4 and Ca 125 to assess the likelihood of malignancy in women with an adnexal mass.

- In premenarcheal girls (infants, children, or adolescents) with an adnexal mass, referral should be made to pediatric gynecology (Hermans et al. 2015).

6 Imaging Studies Interpretation

On pelvic ultrasound adnexal masses may be characterized as simple, cystic, solid, or complex. Asymptomatic simple cysts < 10 cm and CA 125 < 35 u/ml (it drawn) can be managed with close followings regardless of age. (Givens et al. 2009). **According to the American College of Obstetrician and Gynecologists, simple cysts [anechoic, thin wall, smooth, no mural nodules, or septations] up to 10 cm in diameter on ultrasound findings are almost universally benign and may safely be followed without intervention, even in postmenopausal patient** (American College of Obstetrics and Gynecology 2007). The combination of ultrasound plus Doppler flow studies is superior to either alone (Kindel et al. 2005). Typical sonographic appearances of various adnexal masses are shown in Table 3.

Ultrasound [gray scale] should assess:

- Size
- Shape
- Mass characteristics:
  - Solid, cystic, complexity [internal septations [thick or thin], excrescences, papilla, nodules].
  - If ovarian mass is indeterminate (cannot separate benign from malignant condition) on gray-scale ultrasound or if history suggests a possible torsion, color Doppler evaluation is indicated (Kinkel et al. 2000, 2005).

Simple cysts include dominant follicle, arrested follicle, corpus luteum, paraovarian or paratubal cyst, or cystadenomas [ovarian or tubal]. Anechoic cysts with thin septations include two adjacent physiologic cysts, paratubal cyst, hydrosalpinx, peritoneal inclusion cyst, and theca lutein cysts. Cysts with internal echoes but no solid areas include endometrioma, physiologic cyst with hemorrhage, abscess, benign ovarian neoplasm [cystic teratoma, cystadenoma], borderline ovarian tumor, and gastrointestinal duplication cyst or mucocele.

The presence of complexities, mural nodules, or solid mass on ultrasound indicates the need for further studies including MRI, CT, or PET. Benign etiologies of these findings include corpus luteum, mature cystic teratoma, cystadenoma, and ectopic pregnancy. Mostly or completely solid

Table 3 Sonographic appearances of adnexal masses

Benign cyst	Unilocular smooth any size or multilocular smooth <10 cm, no solid components, acoustic shadowing, no blood flow
Endometrioma	Ground glass appearance, often unilocular, varying degrees of echogenicity, medium to low level echoes in a cystic mass, can be small echogenic foci on the cyst wall, a clot may simulate a nodule, and there may be color Doppler flow
Corpus luteum	Thickened wall, small central latency with echoes, circumferential color Doppler flow
Hemorrhagic cyst	Fishnet or reticular pattern [fine network of thin curvilinear echoes], these curvilinear are thin and do not extend across the entire diameter of the cyst [unlike true septa]
Two-simple cysts	Can appear as a single septated cyst
Mature teratoma	May be uniformly hyperechoic or they may have a markedly hyperechoic nodule [with distal acoustic shadowing], some with calcifications or a fluid-fluid level
	Floating globules appear to be predictive; color
	Doppler flow within the cyst makes the diagnosis unlikely
Hydrosalpinx	Tubular in structure, may have structures that look like nodules or incomplete septations [due to folds in the tube], extraovarian in location
	Indentations along opposite walls [waist sign] makes the diagnosis likely
Pedunculated fibroid	Solid, some with cystic portions, hyperechoic, heterogeneous masses, color Doppler can be used to locate a vascular pedicle, separate identification of ipsilateral ovary helpful
Peritoneal inclusion cyst	Septated, cystic masses that can surround bowel or ovary; adhesions appear as bands of tissue with surrounding fluid
Malignancy	**Solid nodular or papillary components that demonstrate color Doppler flow**, not hyperechoic
	Solid irregular multilocular, often 10 cm or more
	Papillary structures [generally more than 4]
	Thick [>2–3 mm] septations
	Presence of ascites
	Other peritoneal masses, enlarged lymph nodes, matted bowel

masses include leiomyoma [pedunculated or in broad ligament], adnexal torsion, epithelial ovarian or tubal carcinoma, ovarian germ cell tumors [teratocarcinoma, struma ovarii], ovarian sex cord-stromal tumors [fibroma, Sertoli-Leydig], metastasis to ovary, and nongynecologic gastrointestinal or neurogenic tumors (Table 1).

7 Management

Management of an adnexal mass is highly dependent on age, pelvic ultrasound findings, pregnancy test, CBC, vital signs, and symptomatology. Evidence-based management guidelines are shown in Table 4.

1. Prepubertal girls with an adnexal mass need immediate referral to a provider experienced in pediatric gynecology.
2. Reproductive aged women:
   (a) A positive pregnancy test, absence of an intrauterine pregnancy [particularly with B-hCG level > 2,000 mIU/ml], and the presence of an adnexal mass indicate a possible ectopic pregnancy. Appropriate and timely medical or surgical intervention or close follow-up is important.
      (i) Pregnant women may also present with an adnexal mass, almost always a luteoma of pregnancy. Luteomas regress after the pregnancy and are associated with complication in less than 2 % of cases.
   (b) Asymptomatic premenopausal women [negative pregnancy test] diagnosed with a simple ovarian cyst <10 cm generally have a follow-up ultrasound in 4–8 weeks. They may be followed for 2–3 months or longer. Oral contraceptives are not effective in the management of functional ovarian cysts in

Table 4 Management guideline (Guidelines 2007)

LEVEL B evidence
In asymptomatic women with pelvic masses, transvaginal ultrasound is the modality of choice
Positive predictive value and specificity of CA-125 is much greater in postmenopausal women compared to premenopausal women
Any elevation of CA-125 in a postmenopausal woman is highly suggestive of malignancy
Simple cysts <10 cm in diameter on ultrasound are almost universally benign and can be followed by serial ultrasounds without intervention, even in postmenopausal women
Unilateral salpingoophorectomy or cystectomy in patients with germ cell tumors, tumors of low malignant potential, and stage 1A1, grade 1–2 invasive cancer who wish to preserve fertility does not appear to associated with compromised prognosis
LEVEL C [consensus or expert opinion]
Most masses in pregnancy appear to have low risk for malignancy or complications and thus can be managed with expectant management
Contraindications
Aspiration of a non-unilocular cyst in a postmenopausal woman is contraindicated
This is because cytology aspirate has poor sensitivity to detect malignancy, aspiration of a malignant mass may cause spilling and seeding of malign cells [changing stage and prognosis], and in approximately 25 % of premenopausal women, the cyst will reoccur. An exception to this is in patients with advanced cancer clinical and diagnostic/radiographic studies who are unfit to undergo surgery; aspiration can be used to confirm diagnosis
If an adnexal mass is suspicious for malignancy based on transvaginal ultrasound findings, CA-125 levels, and clinical assessment, simple laparoscopic surgery is generally contraindicated

premenopausal women (Grimes et al. 2009).

(c) Other findings in premenopausal women:
   1. Fibroids: bleeding control, fertility issues, size, and symptoms determine management.
   2. Possible endometrioma, management dependent on size, fertility issues, and symptoms.
   3. Corpus luteum generally no intervention necessary. Rarely bleeding problems may have to be addressed.
   4. Complex or solid adnexal mass: MRI or CT used to further characterize the lesion. For premenopausal women with a benign diagnosis, management is generally laparoscopic or open cystectomy or oophorectomy depending on findings. Referral to gyn oncology is advised if malignancy is suspected.

3. Postmenopausal women:
   (a) Asymptomatic postmenopausal women with a simple cyst <10 cm are followed expectantly (Modesitt SC 2003).
   (b) Complex masses or solid mass in postmenopausal woman with elevated CA-125 (some reports recommend >35 U/ml) should be referred to gyn oncology.
   (c) Complex masses or sold masses with non-elevated CA-125 and no suspicious ultrasound or MRI/CT findings are generally managed with oophorectomy.
   (d) If a nongynecologic disease is diagnosed, appropriate treatment or referral is indicated.

8 Conclusions

Adnexal masses are a common gynecological problem. Pelvic ultrasound [gray scale] is typically the first-line imaging study in both pre- and postmenopausal women for evaluation of an adnexal mass. Color Doppler evaluation can be added for further characterization (Guidelines 2007).

- The goal of the ultrasound is to determine if the mass is almost certainly benign (Patel et al. 2016) or whether there is some chance of

malignancy [if so, further work-up/imaging studies indicated].

- In reproductive aged women, [physiological] simple cysts are common. Simple cysts have anechoic fluid filling the cyst, thin walls, and no impairment of sound transmission through the cyst.
  - If there are no solid areas in the mass, the chance of malignancy is low.
  - If the simple cyst is greater than 7 cm, MRI may be indicated to accurately assess the cyst [due to size].
    - Oral contraceptives are generally not helpful in shrinking an ovarian cyst (Grimes et al. 2009).
  - Serum Ca-125 should not be used routinely during the work-up of an adnexal mass in a premenopausal patient *(ordered if suspicious findings on ultrasound).* Screening for ovarian cancer with CA 125, transvaginal ultrasonography, and screening pelvic exam are not recommended (US Preventative Task Force 2015).
  - An adnexal mass occurring during a pregnancy has a very low risk of malignancy and can be managed expectantly (Hermans et al. 2015; Bernhard et al. 1999).
  - An adnexal mass suspicious for malignancy as described in Table 3 should be referred to gyn oncology or undergo further testing (multinodal testing) as described below.
- In postmenopausal women, complex masses or solid mass with elevated CA-125 should be referred to gyn oncology.
  - Evaluation of any adnexal mass that has suspicious elements can be further evaluated using MRI or CT scan.
    - Benign lesions such as exophytic myoma and benign cystic teratoma can also be more accurately characterized using MRI.
  - Multinodal testing: repeat ultrasound, Ca-125, MRI, and CT are used to differentiate between benign and malignant adnexal masses when necessary.

8.1 Follow-Up

- Premenopausal
  - Asymptomatic cysts >5–7 cm in premenopausal woman should have yearly ultrasound follow-up.
  - Premenopausal woman with complex features in a cyst that is worrisome, short interval follow-up ultrasound [few weeks or more].
    - Follow-up ultrasound done optimally on menstrual cycle days 7–12.
    - A decrease in size is reassuring.
- Postmenopausal
  - Yearly ultrasound follow-up for postmenopausal with simple cysts <10 cm in size

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