Fertility Preservation and Restoration for Patients with Complex Medical Conditions

Allison L. Goetsch
Dana Kimelman
Teresa K. Woodruff

Springer

Fertility Preservation and Restoration for Patients with Complex Medical Conditions

Allison L. Goetsch • Dana Kimelman
Teresa K. Woodruff

Fertility Preservation and Restoration for Patients with Complex Medical Conditions

Springer

Allison L. Goetsch
Ann and Robert Lurie Children's Hospital
Chicago, Illinois
USA

Dana Kimelman
Northwestern University
Chicago, Illinois
USA

Teresa K. Woodruff
Northwestern University
Chicago, Illinois
USA

ISBN 978-3-319-52315-6 ISBN 978-3-319-52316-3 (eBook)
DOI 10.1007/978-3-319-52316-3

Library of Congress Control Number: 2017932901

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This is the sixth book in a series concerning the medical management of fertility in cases of iatrogenic, traumatic, or genetic loss. *Fertility Preservation and Restoration for Patients with Complex Medical Conditions* is a necessary textbook, largely because there is a wealth of information on fertility preservation for individuals with cancer but a relative paucity of information on the many other diseases where fertility may be compromised. Each of these conditions is nuanced, and many are not sterilizing, but the healthcare professional needs to be aware of the concerns, particularly of the young population, regarding their interests in overall reproductive health. Moreover, the reproductive system is a powerful regulator of overall health influencing bone and cardiovascular health; thus, this book provides important information for primary care to specialist care.

The book includes information on hereditary cancer syndromes, disorders of sex development, hematologic diseases, genetic disorders of gonadal dysfunction, immunologic diseases, gynecologic diseases, endocrine disorders, and autoimmune and inflammatory diseases. The target audience includes primary care physicians as well as specialists such as obstetrician/gynecologists, endocrinologists, immunologists, hematologists, oncologists, gastroenterologists, nephrologists, geneticists, and genetic counselors and physician assistants, nurse practitioners, and may others. Moreover, this book can be used by a variety of medical professionals including medical students, residents, and fellows.

We have organized the chapters into sections that should be useful to each of our medical professionals. We start with the epidemiology of the particular disease and its natural history, highlighting where possible diseases affect younger men and women. We then discuss any classifications of the disease, risk factors, and/or clinical manifestations with diagnosis and treatment modalities. Finally, we discuss the effect of the disease or its treatment on fertility and any options that are specific to that disease condition. The medical management of fertility in complex and chronic disease settings can be very difficult—a drug holiday (tamoxifen holiday) to become pregnant is part of the medical management of breast cancer survivors, but removing the needed drug for IBD or for MS can alter the quality of life or even threaten function. Thus, the provider is urged to discuss fertility matters with the

patient as well as fertility specialists early in the disease management and to keep up to date with changing interests over time. Importantly, there is no one size fits all for cancer patient needs and options, and this is also true in the complex medical condition setting. We include a section on non-biological family building to complement the medical intervention option list, and providers should talk about adoption, fostering, as well as biological parenting as part of a complete discussion.

The intersection between medicine and reproductive health is new in part because we have better ways to treat the primary disease, like cancer, with long-term survival. Reproductive interventions have likewise expanded, providing a much longer list of options that could not have been envisioned in the past.

This book is envisioned as a next step in intellectual and practical information, beginning with *Oncofertility: Fertility Preservation for Cancer Survivors* (eds. Woodruff and Snyder 2007), followed by *Oncofertility: Ethical, Legal, Social, and Medical Perspectives* (eds. Woodruff, Zoloth, Campo-Engelstein and Rodriguez 2010), *Oncofertility Medical Practice: Clinical Issues and Implementation* (eds. Gracia and Woodruff 2012), *Oncofertility Communication: Sharing Information and Building Relationships across Disciplines* (eds. Woodruff, Clayman and Waimey 2014), and *Pediatric and Adolescent Oncofertility: Best Practices and Emerging Technologies* (eds. Woodruff and Gosiengfiao 2017). Complex medical conditions are inherently difficult to manage, and reproductive interventions are often not part of the conversation. With this book, we hope to insert this important dialogue at an early stage in management that will enable full health to chronic conditions. The authors thank Chelsea Castleberry for her excellent editorial assistance. We also thank the Center for Reproductive Health After Disease (P50HD076188) from the National Institutes of Health National Center for Translational Research in Reproduction and Infertility (NCTRI).

Chicago, IL, USA

Allison L. Goetsch, MS, CGC
Dana Kimelman, MD
Teresa K. Woodruff, PhD, DSc

Contents

1 Options for Preserving Fertility 1
Introduction 1
Preserving Male Fertility 1
Preserving Female Fertility 3
Alternative Family Building Options 5
References 5

2 Hereditary Gynecologic Cancer Predisposition Syndromes 7
Introduction 7
Hereditary Breast and Ovarian Cancer 7
Lynch Syndrome 10
Other Gynecologic Hereditary Cancer Predisposition Syndromes 13
References 14

3 Disorders of the Sex Chromosomes and Sexual Development 19
Turner Syndrome (45, X) 19
Incidence 19
Natural History 19
Disease Presentation 20
Ovarian Failure in Turner Syndrome 20
Reproductive Options 21
Turner Syndrome with Mixed Gonadal Dysgenesis (45, X/46, XY) 21
Fertility Preservation Research in Turner syndrome 22
Klinefelter Syndrome (47, XXY) 23
Incidence 23
Natural History 23
Disease Presentation 24
Effect on Fertility 24
Fertility Considerations 24

Y Chromosome Infertility (Contributions from Elizabeth Wignall). 25
Prevalence 25
Natural History 25
Disease Presentation 25
Effect on Fertility 26
Additional Considerations 26
X Chromosome Deletions and Balanced Translocations 26
X Chromosome Deletions in Male Infertility 26
X Chromosome Deletions and Balanced Translocations in Female Infertility 27
Disorders of Sexual Development 27
Gonadal Dysgenesis 28
Ovotesticular Disorders of Sexual Development 28
Testosterone Biosynthesis Defects 30
Androgen Insensitivity Syndrome 33
References 33

4 Malignant Hematologic Diseases 39
Introduction 39
Leukemia 39
Malignant Myeloid Diseases 41
Acute Myelogenous Leukemia (AML) 41
Chronic Myelogenous Leukemia (CML) 42
Malignant Lymphoid Diseases 45
Acute Lymphoblastic Leukemia (ALL) 45
Chronic Lymphocytic Leukemia (CLL) 49
Lymphoma 52
Hodgkin Lymphoma 52
Non-Hodgkin Lymphoma 56
References 57

5 Nonmalignant Hematologic Diseases 61
Hemoglobinopathies 61
Definition 61
Thalassemia 62
Definition 62
Epidemiology 64
Pathophysiology 64
Clinical Manifestations 64
Laboratory Features 67
Differential Diagnosis 67
Treatment 67
Effect on Fertility of Iron Overload 68
Prognosis 71
Prevention 71

Sickle Cell Disease 71
Definition 71
Epidemiology 72
Pathophysiology 72
Laboratory Features 73
Course and Prognosis 73
Clinical Manifestations 73
Treatment 76
Effect on Fertility 77
Fertility Preservation 79
Aplastic Anemia 81
Definition 81
Epidemiology 81
Etiology and Pathophysiology 82
Clinical Features 83
Laboratory Features 84
Natural History 84
Diagnosis 84
Differential Diagnosis 85
Treatment 85
Effect on Fertility and Fertility Preservation Options 87
References 92

6 Genetic Disorders Associated with Gonadal Dysfunction 97
Ataxia-Telangiectasia 97
Incidence 97
Natural History 97
Disease Presentation 97
Disease Management 98
A-T Carriers and Cancer Susceptibility 99
Effect on Fertility 100
Fragile X-Associated Primary Ovarian Insufficiency (FXPOI) 100
Prevalence 100
Natural History 101
Diagnosis 101
Disease Presentation 102
Effect on Fertility 102
Additional Family Planning Considerations 103
Emotional Well-Being 103
Fragile X Carrier Testing 103
Galactosemia 103
Prevalence 103
Natural History 104
Disease Presentation 104
Effect on Fertility 104

GAPO Syndrome 106
22q11.2 Deletion Syndrome 106
Prevalence 106
Natural History 106
Diagnosis. 107
Disease Presentation 107
Effect on Fertility 108
References. 109

7 Inborn Errors of Metabolism. 113
Hematopoietic Stem Cell Transplant 113
Female Fertility After Hematopoietic Stem Cell Transplant 114
Male Fertility After Hematopoietic Stem Cell Transplant 114
Fertility Preservation Considerations 114
Adrenoleukodystrophy 115
Prevalence 115
Natural History 115
Disease Presentation 116
Cerebral Adrenoleukodystrophy 116
Adrenomyeloneuropathy (AMN) 116
“Addison-Only” Presentation 117
Asymptomatic and Presymptomatic Individuals 117
Female Carriers. 117
Effect on Fertility 117
Additional Considerations 118
Alpha-Mannosidosis 118
Prevalence 118
Natural History 118
Disease Presentation 118
Effect on Fertility 119
Aspartylglucosaminidase 120
Prevalence 120
Natural History 120
Disease Presentation 121
Effect on Fertility 121
Fucosidosis 122
Prevalence 122
Natural History 122
Disease Presentation 122
Effect on Fertility 123
Gaucher Disease 123
Prevalence 123
Natural History 123
Disease Presentation 124
Effect on Fertility 124

Hunter Syndrome 124
Prevalence 124
Natural History 124
Disease Presentation 125
Effect on Fertility 125
Hurler Syndrome. 126
Prevalence 126
Natural History 126
Disease Presentation 126
Effect on Fertility 127
Krabbe Disease 128
Prevalence 128
Natural History 128
Disease Presentation 128
Effect on Fertility 129
Lysosomal Acid Lipase Deficiency. 129
Prevalence 129
Natural History 129
Disease Presentation 129
Effect on Fertility 130
Maroteaux–Lamy Syndrome (MPS VI) 131
Prevalence 131
Natural History 131
Disease Presentation 132
Effect on Fertility 132
Morquio Syndrome (MPS IV) 132
Prevalence 132
Natural History 132
Disease Presentation 133
Effect on Fertility 133
Mucolipidosis II 133
Prevalence 133
Natural History 133
Disease Presentation 134
Effect on Fertility 134
Sanfilippo Syndrome (MPS III) 134
Prevalence 134
Natural History 134
Disease Presentation 134
Effect on Fertility 135
Sly Syndrome (MPS VII) 135
Prevalence 135
Natural History 135
Disease Presentation 135
Effect on Fertility 136
References. 136

8 Autoimmune Diseases: Rheumatic Diseases 141
Definition 141
Etiology 141
Prevalence 141
Treatment 142
Fertility Preservation 142
Effect on Fertility and Reproduction 143
Rheumatic Diseases 144
Systemic Lupus Erythematosus 144
Rheumatoid Arthritis (RA) 149
Vasculitis 151
Behcet's Disease (BD) 152
Autoimmune Thyroiditis (AIT) 152
Antiphospholipid Syndrome 153
Sjögren's Syndrome 157
Scleroderma 160
Autoimmune Polyglandular Syndromes (APS) 162
References 163

9 Autoimmune Diseases: Myasthenia Gravis and Multiple Sclerosis 171
Myasthenia Gravis (MG) 171
Definition 171
Physiopathology 171
Incidence 171
Diagnosis 172
Clinical Presentation 172
Treatment 173
Effect on Fertility 173
Multiple Sclerosis 173
Definition 173
Epidemiology 173
Clinical Course 174
Natural History 174
Treatment 174
Effect on Fertility 174
References 177

10 Chronic Kidney Disease 181
Definition 181
Risk Factors for Kidney Failure 181
Clinical Factors 181
Incidence 182
Physiopathology 182
Clinical Manifestations 182

Stages of CKD . . . 183
Epidemiology of Chronic Kidney Disease . . . 183
Etiology of Chronic Kidney Disease . . . 183
Risk Factors for ESRD . . . 183
Evaluation of Cause . . . 184
Treatment . . . 184
Fertility in Women with ESRD . . . 185
Maternal Complications . . . 186
Abnormal Smear Test . . . 186
Contraception . . . 186
Cyclophosphamide . . . 187
Fertility Preservation Options . . . 188
Nephrotic Syndrome . . . 190
Sexual Effects . . . 191
Immunosuppression . . . 192
Fertility in Women on Dialysis and After Successful Transplantation . . . 192
Fertility in Men on Dialysis and After Successful Kidney Transplant . . . 193
References . . . 193

11 Premature Ovarian Insufficiency . . . 197
Incidence . . . 197
Definition . . . 197
Natural History . . . 198
Etiology . . . 198
Disease Presentation . . . 199
Diagnosis . . . 199
Disease Management . . . 203
Bone Protection and Improvement . . . 203
Cardiovascular System Protection . . . 204
Treatment Needs to Focus on Psychological Well-Being and Quality of Life . . . 204
Treatment for Consequences of POI for Sexuality . . . 205
Treatment of Genitourinary Symptoms in POI . . . 205
Medical Treatment . . . 205
Hormone Therapy . . . 205
Effect on Fertility . . . 206
Fertility Preservation . . . 208
References . . . 209

12 Endometriosis . . . 217
Incidence . . . 217
Definition . . . 217
Natural History . . . 217
Disease Presentation . . . 218

Diagnosis. 218
Classification. 219
Disease Management 219
Lifestyle and Dietary Interventions. 220
Medical Treatment 220
Surgical Treatment 221
Effect on Fertility 222
Fertility Preservation. 222
References. 223

13 Uterine Fibroids 227
Prevalence 227
Risk Factors 227
Natural History 228
Clinical Manifestations 228
Effect on Fertility 228
References. 229

14 Polycystic Ovary Syndrome 231
Incidence 231
Definition 231
Natural History 232
Disease Presentation 232
Clinical Expression Usually Includes 232
Hyperandrogenism 232
Hirsutism. 233
Acne 233
Alopecia 233
Ovulatory and Menstrual Dysfunction 233
Polycystic Ovaries. 235
Other Features of the Polycystic Ovary Syndrome. 235
Abnormal Gonadotropin Secretion 235
Insulin Resistance 236
Dyslipidemia. 236
Obesity 236
Metabolic Abnormalities and Associated Health Risks 237
Effect on Mental Health 237
Cancer Risks 237
Effect on Fertility 238
Pathophysiology 238
Diagnosis. 239
Diagnosis in Adolescents 240
Disease Management 240
Management of Women at Risk for T2D 242
Preconceptional Issues and Infertility Treatment 242
Fertility Preservation. 244
References. 244

15 Digestive Autoimmune Diseases: Inflammatory Bowel Disease 249
Incidence 249
Definition 249
Crohn's Disease 250
Ulcerative Colitis 250
Diagnosis. 250
Etiology and Pathophysiology 251
Genetics. 251
Environmental Factors 251
Immune System 252
Disease Presentation 252
Gastrointestinal Symptoms and Extraintestinal Symptoms 252
Gastrointestinal Symptoms Related to Menstrual Cycle 253
Psychological Aspects. 253
Cervical Dysplasia 254
Complications 254
Disease Management 255
Laboratory Tests 255
Medical Treatment 256
Surgery 256
Effect on Fertility 257
Pregnancy Outcomes. 259
Male Fertility 260
IVF Results 260
Fertility Preservation. 260
References. 261

16 Breast Cancer 267
Incidence 267
Natural History 268
Risk Factors 268
Environmental Factors 270
Protective Factors 271
Staging 271
Pathology 271
Screening. 272
Palpable Mass 272
Mammography 272
Diagnosis. 273
Diagnostic Evaluation and Techniques 273
Treatment 275
Local Therapy 275
Systemic Therapy 276
Gene Expression Assays 277

Metastatic Disease 277
Neoadjuvant Chemotherapy 277
Radiation Therapy 277
Breast Reconstruction 277
Effect on Fertility 278
Systemic Therapy and Effect on Reproductive System 279
Fertility Preservation 279
References 281

17 Ovarian Cancer 285
Definition 285
Incidence, Epidemiology, and Etiology 285
Incidence and Mortality 285
Risk Factors 286
Etiology 287
Hereditary Ovarian Cancer 288
Diagnosis 289
Clinical Manifestations 289
Serological Biomarkers: CA 125 290
Ultrasound 290
Differential Diagnosis 290
Staging 291
Survival Is Affected by 291
Guidelines for Staging in Epithelial Ovarian Cancer 291
Treatment 292
Surgical Therapy in Ovarian Cancer 292
Borderline Malignant Epithelial Neoplasms 293
Definition, Incidence, and Epidemiology 293
Treatment 293
Fertility Preservation 294
References 297

18 Endometrial Cancer 301
Definition 301
Incidence 301
Epidemiology 301
Natural History 302
Type 1 Endometrioid Adenocarcinoma 302
Type 2 302
Etiology 303
Clinical Manifestations 304
Diagnosis 304
Fractional Dilation and Curettage (D&C) 305
Endometrial Biopsy 305
Hysteroscopy 305
Ultrasonography (US) 305

Pathology 306
2009 FIGO Staging System for Carcinoma of the Endometrium 306
Endometrial Carcinoma Subtypes 306
Tumor Grade 307
Prognostic Factors 307
Prevention of Endometrial Cancer 307
Lifestyle Modifications 307
Periodic Exposure to Progestins 308
Oral Contraceptives 308
Treatment 308
Management of Atypical Endometrial Hyperplasia (AEH) 308
Management of Hyperplasia Without Atypia 309
Management of Endometrial Cancer 309
Surgical Treatment 309
Chemotherapy 310
Radiation Therapy 310
Follow-Up 310
Effect on Fertility 311
Fertility Preservation 311
References 314

19 Cervical Cancer 319
Epidemiology 319
Natural History 319
Cervical Intraepithelial Neoplasia (CIN) 320
Histologic Classification of Cervical Cancer 320
Epithelial Tumors 320
Nonepithelial Tumors 321
Risk Factors 321
Clinical Manifestations 322
Diagnosis 322
Staging 323
International Federation of Gynecology and Obstetrics 323
Treatment 324
Prevention 324
Vaccination 324
Screening 325
Effect on Fertility 325
Fertility Preservation Options 325
References 326

Index 329

Chapter 1
Options for Preserving Fertility

Introduction

Significant improvements in medical treatments have led to decreased morbidity and mortality among individuals with complex medical conditions. These individuals are living longer, fuller lives. Advances in reproductive medicine now allow individuals with complex medical conditions whose disease or its treatment may impair fertility, to undergo fertility preservation. Fertility preservation options are available for females and males of prepubertal and reproductive age.

In this chapter, we summarize the current fertility preservation options available, including experimental fertility preservation techniques, for both genders. For a more comprehensive overview of fertility preservation techniques, we invite you to read *Oncofertility Medical Practice*.

Preserving Male Fertility

The male testes function to produce testosterone, a steroid hormone that helps regulate and guide male sexual and reproductive development, and sperm cells, the male gamete. Fertility preservation options exist for pubertal males, and experimental fertility preservation options exist for prepubertal males.

Semen cryopreservation, or sperm banking, is the gold standard fertility intervention for males that has gone through puberty or whom will be sexually mature enough to produce a semen specimen. Appropriate candidates for semen cryopreservation include males that are typically Tanner stage III and/or >12 years of age with 1–2 years of puberty. A semen sample is collected by masturbation, mechanical ejaculation, or electroejaculation. Ideally, males will need to provide two specimens, approximately 2–3 days apart. The semen sample will undergo analysis to ensure the specimen contains sperm. If sperm are detected, the sample

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_1

may undergo cryopreservation. If sperm are not detected or the individual is unable to produce a sample, other options should be discussed with the individual and their family. Testicular sperm extraction (TESE) is an option for adolescent and adult males who are unable to produce a semen sample. It is a surgical approach that involves sperm retrieval from a testicular biopsy.

Gonadal shielding is an option for males whose medical treatment involves radiation therapy. It is designed to protect the testes from scatter radiation during treatment.

The only option for prepubertal males who are not producing sperm is testicular tissue cryopreservation. This option is considered experimental; however, the current consensus is that it is reasonable to preserve testicular tissue for young males at high risk for infertility or those who have no other options to preserve their fertility. To date, no spermatogenic recovery or pregnancies from cryopreserved testicular tissue have been reported.

There are several future therapies anticipated for use with cryopreserved testicular tissue. The first method involves isolation of spermatogonial stem cells (SSCs) from the frozen testicular tissue pieces followed by transplantation of SSCs into the seminiferous tubules of an individual's testicles to produce sperm. This is the only method with the potential to restore normal spermatogenesis, or the production of sperm cells, and fertility in individuals whose disease or treatment is known to impair fertility. SSC transplantation was first described and performed in mice by Ralph Brinster and colleagues in 1994, and since then it has successfully been completed in many other animals, including nonhuman primates [1–4]. Human SSC transplantation has been performed; however, fertility status has not been reported [5].

Alternative experimental options to transplanting SSCs include the maturation of spermatozoa in testicular tissue organ culture followed by testicular tissue autografting or xenografting. These methods involve grafting intact testicular tissue pieces to an orthotopic (scrotum) or an ectopic site (e.g., under the skin). Spermatogenesis is initiated, and the sperm can be recovered from the tissue after several weeks. The recovered sperm can be used to fertilize oocytes with use of intracytoplasmic sperm injection (ICSI). Successful production of spermatogenesis and sperm from autografted testicular tissue has been reported in mice and nonhuman primates [6, 7]. Research of interspecies xenografts (e.g., from human to mouse or human to pig) may also be considered.

Future directions for male fertility preservation include in vitro SSC culture, which has the potential to generate millions of stem cells for injection into the testis. This would increase the chance for robust engraftment and initiation of spermatogenesis. Additionally, in vitro spermatogenesis has been proposed as a possible method to produce sperm from frozen tissue or cells. This option would eliminate the need for SSC transplantation or autografting and would eliminate the possible reintroduction of malignant cells for those with cancer. A third potential future fertility preservation method is to create pluripotent-derived male germ cells. Somatic cells, such as the skin or blood, would be stimulated to produce induced pluripotent stem cells (iPSCs), which have the potential to differentiate into transplantable germ cells that may regenerate spermatogenesis. In theory, pluripotent-derived male germ

Table 1.1 Status of experimental and proposed male fertility preservation options

SSC transplant	Attempted in humans, results not reported
SSC culture	Successful human short-term survival and proliferation in vitro
Autografting of testicular tissue	Not reported in humans
Xenografting of testicular tissue	Long-term survival and presence of spermatocytes in prepubertal/adolescent tissue grafts. Limited survival of adult tissue grafts
In vitro maturation of germ cells in organ culture	Not reported in humans
Generation of germ cells from iPS cells	Derivation of human germ cells confirmed by biomarker expression

cells would allow males who did not preserve semen or testicular tissue, the option to have biological children (Table 1.1).

Preserving Female Fertility

The female ovaries function to produce oocytes (eggs), the female gamete. Fertility preservation options, including experimental methods, exist for pubertal and prepubertal females. Selection of appropriate fertility preservation methods should take into consideration the individual's risk for infertility, timing of expected loss of fertility or fertility-threatening treatment, and her pubertal status.

Embryo cryopreservation, also referred to as embryo banking, is an accepted fertility preservation method for pubertal females. The process involves stimulation of the ovaries with fertility hormones over a 10–12-day period to produce eggs. Eggs are removed transvaginally and fertilized through in vitro fertilization with sperm from a partner or donor. The resulting embryos may be frozen until the individual is family planning. At that time, embryos are thawed and implanted into the individuals' or their surrogates' uterus.

Oocyte cryopreservation, also referred to as egg banking, is an accepted fertility preservation method for pubertal females. The process involves stimulation of the ovaries with fertility hormones over a 10–12-day period to produce eggs. Eggs are removed transvaginally and frozen until the individual is family planning. At that time, eggs are thawed and fertilized with partner or donor sperm, and the resulting embryos are implanted into the individuals' or their surrogates' uterus. Most published data demonstrates no difference in fertilization and pregnancy rates among women who used frozen oocytes compared to those with fresh oocytes [8]. The American Society for Reproductive Medicine and the American College of Obstetrics and Gynecology estimate a ~2% live birth rate per thawed oocyte following slow-freeze methods, and a ~4% live birth rate per thawed oocyte following vitrification. The live birth success rate estimates for cryopreserved oocytes are not statistically significant when compared to the live birth success rate for

cryopreserved embryos. Additionally, there is no evidence of increased neonatal risk from oocyte cryopreservation compared with other assisted reproductive technologies [9–11].

Ovarian tissue cryopreservation, or banking, is an experimental method of female fertility preservation, which involves surgical removal of all parts of an ovary. The surgery is generally performed laparoscopic or, for those undergoing radiation therapy, at the time of ovarian transposition surgery. After removal, the outer surface of the ovary, the cortex, is removed and frozen into strips. The ovarian cortex contains most oocytes. Therefore, a small volume of cortical tissue may yield cryopreservation of a large number of oocytes. The thawed ovarian tissue can eventually be transplanted back into the patient to either an orthotopic (e.g., pelvic) or heterotopic (e.g., extrapelvic) site. Pregnancies with live births have been achieved with orthotopic transplantation of cortical strips [12].

In 2014, the Practice Committee of the American Society for Reproductive Medicine released an opinion on ovarian tissue cryopreservation, supporting its experimental use for individuals who require immediate gonadotoxic treatment and/or prepubertal females [12]. Whole ovary cryopreservation is an acceptable method of fertility preservation for females whose reproductive potential is diminished due to their medical condition or its treatment.

Prepubertal and pubertal females whose medical treatment involves radiation therapy may elect to consider radiation shielding to reduce their exposure to radiation. While this process protects ovaries from radiation, it does not protect the ovaries from the effects of other treatments, such as chemotherapy, often used in conjunction with radiation. Alternatively, females anticipating radiation therapy may elect to consider ovarian transposition. Ovarian transposition in a surgical procedure involves moving the ovary to a side in the abdomen or pelvis, outside the radiation field. It decreases the amount of radiation to which the ovaries are exposed, but similarly to radiation shielding, it does not protect the ovaries from the effects of other treatments used in conjunction with radiation.

Ovarian suppression is a fertility preservation option available for pubertal females anticipating short-term treatment or therapy with gonadotoxins. It is not an acceptable option for women with diminished reproductive potential due to their complex medical condition. Ovarian suppression involves use of medications called gonadotropin-releasing hormone analogues (GnRHa). These medications may be used while a pubertal female undergoes a short-term gonadotoxic treatment or therapy. It has been proposed that GnRHa use may decrease ovarian perfusion, suppress pituitary follicle-stimulating hormone (FSH) production, and activate gonadotropin-releasing hormone (GnRH) receptors. There is limited data about the efficacy of ovarian suppression with GnRH to preserve fertility. Randomized control trials have found varying results, with no statistical difference between use and no use of GnRHa [13–16].

Emerging fertility options that require IRB approval include the removal of an ovary or testis biopsy prior to the first treatment [17–19]. The removal of an ovary should only be considered under conditions where there is a very high level of presumed sterility associated with the treatment. If tissue removal is warranted,

there are a variety of options for that cryopreserved tissues including tissue transplant for females. This process has resulted in more than 100 live births and given the absence of cancer cells that reduces the utility of this method for cancer patients can be contemplated. Importantly, the best option for each patient is to maintain the best quality egg in vivo for the longest period of time. Thus, natural pregnancy if possible and hormonal interventions as the second-line option are the best starting point for the provider.

Alternative Family Building Options

Individuals unable to preserve fertility with an established or experimental method, or those who choose not to have biologic children, may consider alternative family building options. Such options include adoption, donor embryos, donor sperm, and donor eggs.

References

1. Zimmermann RBJ. Spermatogenesis following male germ-cell transplantation. Proc Natl Acad Sci U S A. 1994;91(24):11298–302.
2. RL B, Avarbock MR. Germline transmission of donor haplotype following spermatogonial transplantation. Proc Natl Acad Sci U S A. 1994;91(24):11303–7.
3. Hermann B et al. Spermatogonial stem cell transplantation into rhesus testes regenerates spermatogenesis producing functional sperm. Cell Stem Cell. 2012;11(5):715–26.
4. Zheng Y et al. Spermatogonial stem cells from domestic animals: progress and prospects. Reproduction. 2014;147(3):R65–74.
5. Radford J. Restoration of fertility after treatment for cancer. Horm Res. 2003;59(Suppl 1):21–3.
6. Luetjens CM et al. Complete spermatogenesis in orthotopic but not in ectopic transplants of autologously grafted marmoset testicular tissue. Endocrinology. 2008;149(4):1736–47.
7. Wistuba J et al. Meiosis in autologous ectopic transplants of immature testicular tissue grafted to *Callithrix jacchus*. Biol Reprod. 2006;74(4):706–13.
8. Cobo A et al. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod. 2010;25(9):2239–46.
9. Practice Committee of the Society for Assisted Reproductive Technology, Practice Committee of the American Society for Reproductive Medicine. Essential elements of informed consent for elective oocyte cryopreservation: a Practice Committee opinion. Fertil Steril. 2007;88(6):1495–6.
10. ACOG: Committee Opinion No. 584: oocyte cryopreservation. Obstet Gynecol 2014;123(1):221–2.
11. Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013;99(1):37–43.
12. Practice Committee of American Society for Reproductive Medicine. Ovarian tissue cryopreservation: a committee opinion. Fertil Steril. 2014;101(5):1237–43.
13. Del Mastro L et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. JAMA. 2011;306(3):269–76.

14. Badawy A et al. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. Fertil Steril. 2009;91(3):694–7.
15. Gerber B et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011;29(17):2334–41.
16. Kim SS et al. Use of hormonal protection for chemotherapy-induced gonadotoxicity. Clin Obstet Gynecol. 2010;53(4):740–52.
17. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. N Engl J Med. 2009;360(9):902–11.
18. Redig AJ et al. Incorporating fertility preservation into the care of young oncology patients. Cancer. 2011;117(1):4–10.
19. Duncan FE et al. Ovarian tissue transport to expand access to fertility preservation: from animals to clinical practice. Reproduction. 2016;152(6):R201–r210.

Chapter 2
Hereditary Gynecologic Cancer Predisposition Syndromes

Introduction

In the last decade, a great deal of progress has been made in terms of improving clinician–patient education, communication, and decision support with regard to fertility preservation for individuals diagnosed with cancer [1–14]. A different and unique approach must be taken toward individuals with hereditary cancer syndromes who face significantly greater lifetime risk to develop cancer than the general population. In this chapter, we specifically address the unique fertility needs and reproductive options of women with hereditary breast and ovarian cancer (HBOC) syndrome due to *BRCA1/2* mutations and Lynch syndrome due to mutations in *MSH2*, *MLH1*, *MSH6*, *PMS2*, and *EPCAM*. Clear data now exists to indicate that HBOC and Lynch syndrome underlie at least 20% of all ovarian cancer diagnoses [15].

Hereditary Breast and Ovarian Cancer

Women with hereditary breast and ovarian cancer (HBOC) have mutations in *BRCA1* and *BRCA2*, which confer a significantly greater lifetime risk of developing breast and ovarian cancer than the general population (Table 2.1) [16]. Additionally, the average age of breast and ovarian cancer diagnosis in women with *BRCA1/2* pathogenic variants is significantly younger than that in the general population [17].

Prophylactic bilateral salpingo-oophorectomy (PBSO) is an established ovarian cancer prevention strategy known to reduce the incidence of ovarian cancer by greater than 80% in women at increased risk [31, 32]. This risk reduction held true among women with *BRCA1/2* mutations; PBSO was reported to be associated with an 80% reduction in risk of ovarian, fallopian tube, or peritoneal cancer, and a 77% reduction in all-cause mortality among women with HBOC [33]. The National Comprehensive Cancer Network (NCCN) recommends for women with HBOC

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_2

Table 2.1 Lifetime cancer risks for *BRCA1/2* mutation carriers compared to the general population

Type of cancer[a]	Lifetime risk for *BRCA1* mutation carriers	Lifetime risk for *BRCA2* mutation carriers	Lifetime risk for general population
Female breast cancer	47–66% [18][b]	40–57% [19][b]	12% [20]
Second primary female breast cancer within 5 years	10% [21]	5% [21]	3% [22]
Second primary female breast cancer within 25 years	48% [21]	47% [21]	12% [22][c]
Ovarian cancer	35–46% [16]	12–23% [16]	1% [20]
Male breast cancer	1% [23]	7% [23]	0.04% [24]
Prostate cancer	9% [25][d]	20% [26]	17% [27]

[a]There are inconsistent published results regarding the association between *BRCA2* mutation and elevated risks of pancreatic cancer and melanoma compared with the general population [28–30]
[b]Denotes risk by age 70
[c]Denotes 20-year risk
[d]Denotes risk by age 65

risk-reducing PBSO to occur ideally between age 35 and 40 years, after completion of childbearing, or based on the earliest age of onset of ovarian cancer in the family [34]. Without PBSO, approximately 3% of women with *BRCA1* mutations are diagnosed with ovarian cancer by age 40 years, and 21% of women with *BRCA1* mutations are diagnosed with ovarian cancer by age 50 years [35, 36]. Of those women with HBOC who elect to undergo PBSO, a 3–4% risk of primary peritoneal cancer remains [31, 37].

As high as 70% of eligible *BRCA1/2* mutation, carriers elect to undergo PBSO to reduce personal cancer risk [33, 38, 39]. Cancer risk reduction is greater if PBSO is performed before the age of 40 years [33, 39]. For this reason, young women with *BRCA1/2* mutations often must make the decision to undergo PBSO—either after a cancer diagnosis or as a prophylactic procedure in anticipation of a cancer diagnosis—at the same time that they are planning to have a family.

One of the side effects of premenopausal PBSO is immediate menopause. Given that many women with *BRCA1/2* mutations elect to undergo PBSO, Kotsopoulos et al. (2016) sought to clarify whether or not the use of hormone replacement therapy (HRT) to mitigate menopausal symptoms is safe in women with HBOC and no personal cancer history. They conducted a case-control analysis of 432 matched pairs of women with *BRCA1* mutations. Kotsopoulos et al. (2016) found no evidence that a short course of HRT should be contraindicated among women with *BRCA1* mutations and no personal history of cancer. Therefore, HRT may be considered after PBSO to mitigate menopausal symptoms among women with *BRCA1* mutations. This study did not analyze *BRCA2* mutation carriers [40].

Of note, research has suggested that woman with *BRCA1/2* mutations may have compromised fertility and are at increased risk for early menopause. This information should be taken into consideration when discussing prophylactic surgery, fertility

preservation, and/or family planning options with women with HBOC. *BRCA1/2* mutations may have a negative effect on the ovarian reserve by causing early oocyte apoptosis and depletion, ultimately leading to premature menopause [41]. Additionally, several population studies have shown that women with *BRCA1/2* begin menopause at an earlier age than the general population [37, 42]. Giordano et al. (2016) further evaluated the connection between infertility and breast and ovarian cancer risk among women with *BRCA1* mutations. They evaluated 124 women ages 18–45 years to see if there was an association between anti-Mullerian hormone (AMH) levels, age, and presence of a *BRCA1* mutation. They defined low AMH levels as <0.05 ng/mL. They found that women with *BRCA1* mutations had significant decline in AMH levels with age ($p = 0.0011$), and women with *BRCA1* mutations who were older than 35 years of age had ten times the odds of low AMH levels compared to those 35 years of age and younger. Giordano et al. (2016) concluded that women older than 35 with *BRCA1/2* mutations have lower AMH levels and therefore decreased ovarian reserve, than women without *BRCA1/2* mutations. Young adults with *BRCA1* mutations should be counseled regarding their potential decrease in ovarian reserve when discussing prophylactic surgery, fertility preservation, and/or family planning [43].

BRCA1/2 mutation-positive status does not seem to affect the decision to have a child [44], and although *BRCA1/2*-positive women can pursue other possible avenues to parenthood, such as adoption and third-party reproduction, the literature indicates that these women prefer to have biological offspring [45, 46]. Women with HBOC have the option to undergo fertility preservation procedures such as embryo cryopreservation [2] or oocyte cryopreservation [47], but they may have an additional concern about passing on hereditary cancer susceptibility to their future children [2]. HBOC is an autosomal dominant genetic disorder with a recurrence risk of 50% with each pregnancy. To reduce this risk, patients may pursue preimplantation genetic diagnosis (PGD) and embryo selection, which have been used in conjunction with in vitro fertilization (IVF) to screen for *BRCA1/2* mutations since 2006 [2].

Previous studies have assessed HBOC patient attitudes toward PGD. Women with *BRCA1/2* mutations report a lack of available information about the process and procedures of PGD and fertility preservation [48]. In fact, 65–80% of individuals have no knowledge of PGD prior to participating in PGD attitude studies [49, 50]. Once informed, the overwhelming majority of study participants agree that individuals with HBOC should be provided with information about PGD and that PGD is an acceptable option for women with *BRCA1/2* pathogenic variants [49, 50]. Women with *BRCA1/2* pathogenic variants also express a strong desire for assistance with oncofertility and PGD decision-making [48]. Furthermore, a qualitative study assessing couples' experiences with PGD for *BRCA1/2* mutations found the emotional impact of the decision whether or not to have PGD was substantial and long-lasting, underscoring the need for reproductive counseling and additional decision support [51]. The lack of knowledge and desire for more PGD information and decision support in the HBOC community suggests the need for the development of patient decision aids and educational materials. Ultimately, *BRCA1/2*-positive

women need to be aware that oncofertility services, like fertility preservation and PGD, are available to them.

Lynch Syndrome

Lynch syndrome is a hereditary cancer predisposition syndrome often referred to as hereditary nonpolyposis colorectal cancer (HNPCC). The distinction between Lynch syndrome and HNPCC is that all individuals with Lynch syndrome have mutations in *MSH2*, *MLH1*, *MSH6*, and *PMS2* or a constitutional 3'-end deletion of *EPCAM* (upstream of *MSH2*), which confer a significantly greater lifetime of developing certain cancers, specifically colorectal and endometrial cancers, compared to the general population (see Table 2.2) [52–54]. Individuals with Lynch syndrome are also at increased risk to develop the following cancers: ovarian, stomach, hepatobiliary tract, urinary tract, small bowel, brain, central nervous system, and sebaceous neoplasms [55]. Additionally, the average age of cancer diagnosis in individuals with Lynch syndrome is younger than the general population [56].

Lynch syndrome is generally underdiagnosed [65] and accounts for approximately 2–5% of all colorectal cancer cases [66, 67]. Most individuals are diagnosed after a cancer diagnosis, as the revised Bethesda guidelines recommend further molecular analysis of tumors among patients with colorectal cancer by MSI/immunohistochemistry [68]. For simplicity, some have recommended symptomatic testing of all patients with colorectal cancer or all individuals with colorectal cancer under 70 years of age by MSI/immunohistochemistry independent of clinical criteria [69]. With the increase of genetic testing and genetic counseling, more individuals are being diagnosed with Lynch syndrome prior to a cancer diagnosis and therefore require screening for associated malignancies.

Individuals with Lynch syndrome undergo routine colonoscopies due to their significantly greater lifetime risk to develop colorectal cancer than the general population. Current guidelines recommend colonoscopies every 1–2 years for individuals with Lynch syndrome and no history of colorectal cancer. As there is a substantial risk to develop a second primary colorectal cancer after partial colectomy and similar quality of life after partial and subtotal colectomy, the option of subtotal

Table 2.2 Lifetime cancer risks for individuals with Lynch syndrome compared to the general population

Type of cancer	Lifetime risk for individuals with Lynch syndrome	Lifetime risk for general population
Colorectal cancer	25–70% [55]	4.8% [57]
Endometrial cancer	30–70% [58–61]	2.7% [57]
Ovarian cancer	3–20% [58, 59, 62–64]	1% [57]

Limited to the three most common diagnoses

colectomy should be discussed with all individuals with Lynch syndrome and colorectal cancer, particularly with younger patients [55].

The risk to develop endometrial cancer is very high and equals or exceeds the risk of colorectal among women with Lynch syndrome [59]. The average age of endometrial cancer diagnosis among women is reportedly between ages 48 and 54 years [70, 71]. Current endometrial cancer screening guidelines recommend women with Lynch syndrome be offered transvaginal ultrasound and aspiration biopsy starting at age 35–40 years as a cancer risk-reducing strategy [55]. However, the value of endometrial surveillance is largely unknown. The benefits of screening include possible identification of precursor lesions of endometrial cancer as well as possible, but unproven, identification of early stage endometrial cancer. In contrast, the cons of screening include the physical burden of surveillance examination, especially by pipelle biopsy, small risk of death as with any procedure, psychological burden, and lack of evidence of efficacy for early stage cancer detection [55].

It has been suggested that the most effective cancer risk-reducing strategy among women with Lynch syndrome is risk-reducing hysterectomy with BSO [64]. In a study of 315 women with Lynch syndrome, 61 underwent prophylactic hysterectomy with BSO, and in long turn follow-up, none developed endometrial or ovarian cancer. Among the women who did not undergo prophylactic surgery, 33% developed endometrial cancer, and 5.5% developed ovarian cancer [72]. Multiple modeling studies have shown that prophylactic hysterectomy and BSO can significantly reduce the risk of endometrial cancer [72], increase life expectancy, and be cost-effective for women with Lynch syndrome [73–75].

Ovarian cancer is the third most common cancer among women with Lynch syndrome [76]. Risk estimates range from 3 to 20% [58, 59, 62–64], with current guidelines estimating an overall risk of 9% [55]. The average age of ovarian cancer diagnosis among women with Lynch syndrome is reportedly between 40 and 47 years of age [58, 59, 77, 78]. Additionally, there may be better prognoses for individuals with Lynch syndrome diagnosed with ovarian cancer—Grindedal et al. (2010) found prospectively diagnosed cases of ovarian cancer had a 10-year survival of 81% [79].

Currently, no current consensus exists for optimal surveillance for Lynch syndrome-associated ovarian cancer. Current guidelines for women who meet the criteria for HNPCC include transvaginal ultrasound with serum CA125 every 1–2 years beginning between ages 30 and 35 years [80–82]. There is a limited evidence to determine if routine screening with serum CA125 levels would result in a decrease in mortality for women with Lynch syndrome. CA125 levels may not be a reliable screening technique for women with Lynch syndrome as elevated levels are also associated with benign pelvic disease, such as endometriosis, adenomyosis, and myomas [83].

Prophylactic bilateral salpingo-oophorectomy (PBSO) is an established ovarian cancer prevention strategy known to reduce the incidence of ovarian cancer by greater than 80% in women at increased risk [31, 32]. In 2006, risk-reducing PBSO was accepted as an effective strategy for preventing ovarian cancer among women with Lynch syndrome [72]. The revised Lynch syndrome guidelines, published in

2013, recommend risk-reducing PBSO be an option to be discussed with women with Lynch syndrome who have completed their families, especially after the age of 40 years [55]. Other publications have recommended PBSO at the age of menopause (Lindor et al. 2006). Debniak et al. (2015) suggest risk-reducing PBSO be considered at an earlier age for women with Lynch syndrome. They compared the 10-year-survival rate between women with Lynch syndrome and ovarian cancer and women of Polish ancestry with ovarian cancer and found that risk-reducing PBSO performed at age 35 years would save at least six women from their Lynch syndrome study population [84]. Debniak et al. (2015) conclude that PBSO for women with Lynch syndrome be recommended after 35 years of age as a risk-reducing option due to the increased risk of ovarian cancer, conflicting data regarding prognosis, and lack of gynecologic screening benefit [84]. An earlier study by Schmeler et al. (2006) found that 6% of endometrial cancer and 17% of ovarian cancer were diagnosed prior to age 35 years in their Lynch syndrome study population [72]. Women with Lynch syndrome may wish to pursue prophylactic hysterectomy and/or BSO prior to age 35 years. Additionally, in post-prophylactic surgery, women with Lynch syndrome may wish to consider annual transvaginal ultrasound with serum CA125 or HE4 marker levels to continue to screen for possible risk of primary peritoneal cancers [84, 85].

Discussion of prophylactic surgery with premenopausal women with Lynch syndrome should include a detailed discussion of adverse effects, including immediate onset of menopause, vasomotor symptoms, possible sexual dysfunction, and increased risk of osteoporosis [55]. Hormone replacement therapy can be prescribed for premenopausal women after PBSO to reduce their vasomotor symptoms [86]. Another concern is that pelvic surgery makes colonoscopy screening more difficult and painful. Individuals with previous pelvic surgery may not be able to have a full colonoscopy. Additionally, 10–20% of individuals with Lynch syndrome undergoing PBSO experience psychosocial problems. In conclusion, the revised guidelines recommend hysterectomy and bilateral oophorectomy to prevent the development of endometrial and ovarian cancer be discussed with all women with Lynch syndrome, especially those over the age of 40 years and have completed their families. For those scheduled to undergo colorectal surgery, the option to pursue simultaneous prophylactic hysterectomy with BSO should be considered [55].

Lynch syndrome is inherited in an autosomal dominant manner, conferring a recurrence risk of 50% with each pregnancy [87]. Diagnosis may impact reproductive decision-making, with respect to timing of family planning and concern to pass on the condition to their future children. Individuals with Lynch syndrome may be interested in preimplantation genetic diagnosis (PGD) or prenatal testing [88], although prenatal testing for adult onset conditions is not typically available in the United States. Dewanwala et al. (2011) found that among individuals with Lynch syndrome, 42% would consider using prenatal testing. Additionally, one in five individuals with Lynch syndrome reported they would consider having children earlier in life in order to proceed with prophylactic hysterectomy and/or BSO. Similar to the HBOC population, the Lynch syndrome population in Dewanwala et al.

(2010) study felt it was ethical to offer prenatal genetic testing and PGD for Lynch syndrome; however, only a minority reported they would consider it for themselves [89]. Current Lynch syndrome guidelines recommend geneticists and genetic counselors discuss reproductive options and availability of assisted reproductive technologies with all individuals with Lynch syndrome of childbearing age [55].

Other Gynecologic Hereditary Cancer Predisposition Syndromes

Approximately 5% of all ovarian cancers are due to a mutation in a gene other than *BRCA1/2* or the Lynch syndrome genes [90, 91]. While these other genetic disorders are known to confer a greater risk of developing gynecologic cancers, no specific guidelines exist regarding screening and/or prophylactic surgery, primarily due to insufficient evidence [15, 92]. These conditions include the Li–Fraumeni syndrome, Peutz–Jeghers syndrome, Cowden syndrome, hereditary leiomyomatosis and renal cell carcinoma syndrome, and Fanconi anemia pathway. Additional genes have been identified, in which mutations confer moderate disease risk; no current guidelines exist regarding surveillance and screening [15].

Li–Fraumeni syndrome (LFS) is caused by mutations in *TP53*. LFS is associated with an increased risk for many cancers, including premenopausal breast cancer, ovarian cancer, and endometrial cancer [93]. Leukemia, brain tumors, soft tissue and osteosarcomas, adrenal cortical carcinomas, and bronchoalveolar lung carcinomas have also been reported [93]. LFS is a highly penetrant condition, meaning that virtually 100% of individuals develop cancer. However, it has been suggested that an attenuated Li–Fraumeni-like syndrome (LFLS) may exist with an earlier median age of onset for ovarian cancer of 39.5 years versus 64.3 years [93].

Peutz–Jeghers syndrome (PJS) is caused by mutations in *STK11*, a tumor-suppressor gene. This is a rare condition, affecting approximately one in every 20,000 individuals. PJS is characterized by mucocutaneous pigmentation, gastrointestinal hamartomas, and an increased risk for breast, ovarian, and cervical cancers [15]. Ovarian cancer in PJS can include benign sex cord tumors with annular tubules [94], dysgerminomas, granulosa cell, Brenner, and Sertoli cell tumors. They are often multifocal, bilateral, and small in size [94]. PJS is also associated with a 15–20% lifetime risk of adenoma malignum of the cervix, also referred to as minimal deviation adenocarcinoma (MDA), with a mean age of onset of 33 years compared to 55 years in the general population.

Cowden syndrome is caused by mutations in *PTEN*. Individuals with Cowden syndrome tend to have macrocephaly, skin lesions (i.e., trichilemmomas, lipomas), uterine fibroids, and thyroid disorders. They have a significant increased risk of developing endometrial, breast, and thyroid cancer as well as mixed polyposis of the small and large intestines. The risk to develop endometrial cancer may be as high as 28% [95].

Hereditary leiomyomatosis and renal cell carcinoma are caused by mutations in *FH*. IT is associated with an increased risk of type 2 papillary renal cell carcinoma and uterine tumors, including leiomyomas and leiomyosarcomas [96].

Mutations in genes along the Fanconi anemia pathway have also been linked to moderate to high risk of breast cancer, and more recently to an increased risk of ovarian cancer [15]. *RAD51C*, *RAD51D*, *RAD50*, *BRIP1*, *NBS*, and *MRE11* are critical to the homologous recombination and repair of double-stranded DNA breaks. Mutations in *RAD51C* have been reported to have a lifetime risk of ovarian cancer of 9% or a relative risk of 6.3 (95% CI 2.9–13.9) [97]. Mutations in *BRIP1* are associated with a lifetime risk of invasive epithelial ovarian cancer of 6% or a relative risk of 11–14 [97]. Additionally, mutations in *MRE11*, *NBS1*, and *RAD50* appear to be associated with an increased risk of ovarian cancer [98].

Women with hereditary predispositions to gynecologic cancer, other than HBOC and Lynch syndrome, considering PBSO, should consider the benefits, risks, and limitations of surgery. Fertility preservation and family planning options like PGD, including 50% recurrence risk with each pregnancy, should be discussed with all women undergoing prophylactic cancer risk-reducing surgery that impacts fertility.

References

1. Loren AW et al. Fertility preservation for patients with cancer: American society of clinical oncology clinical practice guideline update. J Clin Oncol. 2013;31(19):2500–10.
2. Quinn GP et al. Frozen hope: fertility preservation for women with cancer. J Midwifery Womens Health. 2010;55(2):175–80.
3. Dillon KE, Gracia CR. Pediatric and young adult patients and oncofertility. Curr Treat Options Oncol. 2012;13(2):161–73.
4. Forman EJ, Anders CK, Behera MA. A nationwide survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. Fertil Steril. 2010;94(5):1652–6.
5. Gardino SL, Jeruss JS, Woodruff TK. Using decision trees to enhance interdisciplinary team work: the case of oncofertility. J Assist Reprod Genet. 2010;27(5):227–31.
6. Hulvat MC, Jeruss JS. Maintaining fertility in young women with breast cancer. Curr Treat Options Oncol. 2009;10(5–6):308–17.
7. Jeruss JS, Woodruff TK. Preservation of fertility for cancer patients. N Engl J Med. 2009;360:902–11.
8. Jungheim ES, Carson KR, Brown D. Counseling and consenting women with cancer on their oncofertility options: a clinical perspective. Cancer Treat Res. 2010;156:403–12.
9. Kesic V et al. Fertility preserving management in gynecologic cancer patients: the need for centralization. Int J Gynecol Cancer. 2010;20(9):1613–9.
10. Lee S et al. Fertility preservation in women with cancer. Clin Exp Reprod Med. 2012;39(2):46–51.
11. Letourneau JM et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012;118:1710–7.
12. Peate M et al. It's now or never: fertility-related knowledge, decision-making preferences, and treatment intentions in young women with breast cancer--an Australian fertility decision aid collaborative group study. J Clin Oncol. 2011;29(13):1670–7.

13. Petru E. Fertility preservation and infertility treatment in breast cancer patients. Wien Med Wochenschr. 2010;160(19–20):487–92.
14. Practice Committee of American Society for Reproductive, M. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2013;100(5):1214–23.
15. Hall MJ et al. Genetic testing for hereditary cancer predisposition: BRCA1/2, Lynch syndrome, and beyond. Gynecol Oncol. 2016;140(3):565–74.
16. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25(11):1329–33.
17. Miesfeldt S, Lamb A, Duarte C. Management of genetic syndromes predisposing to gynecologic cancers. Curr Treat Options Oncol. 2013;14(1):34–50.
18. Coursera. Johns hopkins university. Data science. [cited 27 Mar 2017]. Available from: https://www.coursera.org/specialization/jhudatascience/1.
19. Abdel-Rahman MY et al. Polycystic ovary syndrome and diabetes screening: a survey of gynecologists and reproductive endocrinologists. Eur J Obstet Gynecol Reprod Biol. 2012;162(2):178–81.
20. American Cancer Society. Cancer facts & figures. 2013. [cited 2 Apr 2014]. Available from: http://www.cancer.org/research/cancerfactsfigures/cancerfactsfigures/cancer-facts-figures-2013.
21. Graeser MK et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2009;27(35):5887–92.
22. Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. Int J Radiat Oncol Biol Phys. 2003;56(4):1038–45.
23. Petrucelli N, Daly MB, Feldman GL. Hereditary breast and ovarian cancer due to mutations in BRCA1 and BRCA2. Genet Med. 2010;12(5):245–59.
24. Deb S et al. Genotypic and phenotypic analysis of familial male breast cancer shows under representation of the HER2 and basal subtypes in BRCA-associated carcinomas. BMC Cancer. 2012;12:510.
25. Leongamornlert D et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer. 2012;106(10):1697–701.
26. Castro E, Eeles R. The role of BRCA1 and BRCA2 in prostate cancer. Asian J Androl. 2012;14(3):409–14.
27. American Cancer Society. What are the key statistics about prostate cancer?. 2013. [cited 2 Apr 2014]. Available from: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics.
28. Berliner JL et al. NSGC practice guidelines: risk assessment and genetic counseling for hereditary breast and ovarian cancer. J Genet Couns. 2013;22:155–63.
29. Lowery MA et al. An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions. Oncologist. 2011;16(10):1397–402.
30. van Asperen C., et al. Netherlands Collaborative Group on Hereditary Breast Cancer (HEBON). Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 42(9):711–719.
31. Rebbeck TR et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346(21):1616–22.
32. Kauff ND et al. Risk of ovarian cancer in BRCA1 and BRCA2 mutation-negative hereditary breast cancer families. J Natl Cancer Inst. 2005;97(18):1382–4.
33. Finch APM et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32:1547–53.
34. National Comprehensive Cancer Network. Genetic/Familial high-risk assessment: breast and ovarian. 2013. [cited 2 Apr 2014]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf.

35. King MC et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;302(5645):643–6.
36. Ford D et al. Risks of cancer in BRCA1-mutation carriers. Breast cancer linkage consortium. Lancet. 1994;343(8899):692–5.
37. Finch A et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA. 2006;296(2):185–92.
38. Bradbury A et al. Uptake and timing of bilateral prophylactic salpingo-oophorectomy among BRCA1 and BRCA2 mutation carriers. Genet Med. 2008;10(3):161–6.
39. Eisen A et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol. 2005;23(30):7491–6.
40. Kotsopoulos J et al. Hormone replacement therapy after menopause and risk of breast cancer in BRCA1 mutation carriers: a case-control study. Breast Cancer Res Treat. 2016;155(2):365–73.
41. Oktay K et al. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. J Clin Oncol. 2010;28(2):240–4.
42. Lin WT et al. Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic-based sample of women in northern California. Cancer. 2013;119(9):1652–9.
43. Giordano S et al. Association of BRCA1 mutations with impaired ovarian reserve: connection between infertility and breast/ovarian cancer risk. J Adolesc Young Adult Oncol. 2016;5:337–43.
44. Dekeuwer C, Bateman S. Much more than a gene: hereditary breast and ovarian cancer, reproductive choices and family life. Med Health Care Philos. 2013;16(2):231–44.
45. Crockin S. Legal isses related to parenthood after cancer. J Natl Cancer Inst Monogr. 2005;34:111–2.
46. Schover LR. Patient attitudes toward fertility preservation. Pediatr Blood Cancer. 2009;53(2):281–4.
47. ACOG. ACOG committee opinion No. 413: age-related fertility decline. Obstet Gynecol. 2008;112:409–11.
48. Quinn GP et al. BRCA carriers' thoughts on risk management in relation to preimplantation genetic diagnosis and childbearing: when too many choices are just as difficult as none. Fertil Steril. 2010;94(6):2473–5.
49. Vadaparampil ST et al. Factors associated with preimplantation genetic diagnosis acceptance among women concerned about hereditary breast and ovarian cancer. Genet Med. 2009;11(10):757–65.
50. Quinn GP et al. High-risk consumers' perceptions of preimplantation genetic diagnosis for hereditary cancers: a systematic review and meta-analysis. Genet Med. 2012;14(2):191–200.
51. Derks-Smeets IA et al. Decision-making on preimplantation genetic diagnosis and prenatal diagnosis: a challenge for couples with hereditary breast and ovarian cancer. Hum Reprod. 2014;29:1103–12.
52. Tutlewska K, Lubinski J, Kurzawski G. Germline deletions in the EPCAM gene as a cause of Lynch syndrome - literature review. Hered Cancer Clin Pract. 2013;11(1):9.
53. Ligtenberg MJ et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nat Genet. 2009;41(1):112–7.
54. Kovacs ME et al. Deletions removing the last exon of TACSTD1 constitute a distinct class of mutations predisposing to Lynch syndrome. Hum Mutat. 2009;30(2):197–203.
55. Vasen HF et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut. 2013;62(6):812–23.
56. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med. 2003;348(10):919–32.
57. American Cancer Society. Cancer facts & figures 2013. Atlanta: American Cancer Society; 2013.
58. Aarnio M et al. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer. 1995;64(6):430–3.

59. Quehenberger F, Vasen HF, van Houwelingen HC. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. J Med Genet. 2005;42(6):491–6.
60. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand. 2011;90(5):437–44.
61. Barrow PJ et al. The spectrum of urological malignancy in Lynch syndrome. Fam Cancer. 2013;12(1):57–63.
62. Hampel H et al. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. Gastroenterology. 2005;129(2):415–21.
63. Barrow E et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. Clin Genet. 2009;75(2):141–9.
64. Stuckless S et al. The phenotypic expression of three MSH2 mutations in large Newfoundland families with Lynch syndrome. Fam Cancer. 2007;6(1):1–12.
65. Trano G et al. Awareness of heredity in colorectal cancer patients is insufficient among clinicians: a Norwegian population-based study. Colorectal Dis. 2009;11(5):456–61.
66. Aaltonen L et al. Explaining the familial colorectal cancer risk associated with mismatch repair (MMR)-deficient and MMR-stable tumors. Clin Cancer Res. 2007;13(1):356–61.
67. Aarnio M. Clinicopathological features and management of cancers in lynch syndrome. Patholog Res Int. 2012;2012:350309.
68. Umar A et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96(4):261–8.
69. Hampel H et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med. 2005;352(18):1851–60.
70. Rodriguez-Bigas MA, Moeslein G. Surgical treatment of hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome). Fam Cancer. 2013;12(2):295–300.
71. Hendriks YM et al. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterology. 2004;127(1):17–25.
72. Schmeler KM et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354(3):261–9.
73. Yang KY et al. A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) Families. Fam Cancer. 2011;10(3):535–43.
74. Kwon JS et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. Cancer. 2008;113(2):326–35.
75. Chen LM et al. Gynecologic cancer prevention in Lynch syndrome/hereditary nonpolyposis colorectal cancer families. Obstet Gynecol. 2007;110(1):18–25.
76. Pande M et al. Cancer spectrum in DNA mismatch repair gene mutation carriers: results from a hospital based Lynch syndrome registry. Fam Cancer. 2012;11(3):441–7.
77. Engel C et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012;30(35):4409–15.
78. Ketabi Z et al. The results of gynecologic surveillance in families with hereditary nonpolyposis colorectal cancer. Gynecol Oncol. 2014;133(3):526–30.
79. Grindedal EM et al. Survival in women with MMR mutations and ovarian cancer: a multicentre study in Lynch syndrome kindreds. J Med Genet. 2010;47(2):99–102.
80. Lindor NM et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA. 2006;296(12):1507–17.
81. Schmeler KM, Lu KH. Gynecologic cancers associated with Lynch syndrome/HNPCC. Clin Transl Oncol. 2008;10(6):313–7.
82. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control. 2009;16(1):14–22.
83. Karlan BY, Platt LD. Ovarian cancer screening. The role of ultrasound in early detection. Cancer. 1995;76(10 Suppl):2011–5.

84. Debniak T et al. Management of ovarian and endometrial cancers in women belonging to HNPCC carrier families: review of the literature and results of cancer risk assessment in Polish HNPCC families. Hered Cancer Clin Pract. 2015;13(1):3.
85. Schmeler KM et al. Primary peritoneal cancer after bilateral salpingo-oophorectomy in two patients with Lynch syndrome. Obstet Gynecol. 2010;115(2 Pt 2):432–4.
86. Madalinska JB et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol. 2006;24(22):3576–82.
87. Lynch HT et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet. 2009;76(1):1–18.
88. Clancy T. A clinical perspective on ethical arguments around prenatal diagnosis and preimplantation genetic diagnosis for later onset inherited cancer predispositions. Fam Cancer. 2010;9(1):9–14.
89. Dewanwala A et al. Attitudes toward childbearing and prenatal testing in individuals undergoing genetic testing for Lynch syndrome. Fam Cancer. 2011;10(3):549–56.
90. Pal T et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer. 2005;104(12):2807–16.
91. Walsh T et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011;108(44):18032–7.
92. Daly MB et al. National comprehensive cancer network. J Natl Compr Canc Netw. 2014;12:1326–38.
93. Kamihara J, Rana HQ, Garber JE. Germline TP53 mutations and the changing landscape of Li-Fraumeni syndrome. Hum Mutat. 2014;35(6):654–62.
94. Young RH et al. Ovarian sex cord tumor with annular tubules: review of 74 cases including 27 with Peutz-Jeghers syndrome and four with adenoma malignum of the cervix. Cancer. 1982;50(7):1384–402.
95. Tan MH et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400–7.
96. Toro JR et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet. 2003;73(1):95–106.
97. Meindl A et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet. 2010;42(5):410–4.
98. Heikkinen K et al. Mutation screening of Mre11 complex genes: indication of RAD50 involvement in breast and ovarian cancer susceptibility. J Med Genet. 2003;40(12):e131.

Chapter 3
Disorders of the Sex Chromosomes and Sexual Development

Turner Syndrome (45, X)

Incidence

Turner syndrome (TS) is the most common sex chromosome disorder with an incidence of 1/2500 live-born females. This condition occurs with a similar frequency in all populations [1].

Natural History

Turner syndrome is a developmental disorder caused by the absence or structural abnormality of a sex chromosome, typically an X chromosome. This syndrome is an instance of monosomy, and it is the only monosomy considered to be compatible with life. The karyotype of a girl with classic Turner syndrome is typically (45, X) (instead of 46, XX or 46, XY).

Some individuals with Turner syndrome have mosaicism, which occurs when not all cells in the body are missing the second X chromosome [1, 2]. The most common mosaic karyotype is 46, XX/45, X; however, additional mosaic karyotypes exist involving one cell line containing 45, X. Some individuals with mosaic Turner syndrome may have a cell line containing Y chromosome material. It is important to identify Y chromosome material, as it may alter medical management.

Current estimates suggest 5% of individuals with Turner syndrome have a cell line containing a Y chromosome, while 3% contain a cell line with a marker chromosome of X or Y chromosome origin [3, 4]. Chromosome analysis may not reveal presence of Y chromosome material in as many as 5–15% of individuals with

Contributions from Rikki Gaber, MS, CGC

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_3

Turner syndrome; therefore, polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) analysis is recommended for detection of Y chromosome material [5, 6].

Disease Presentation

Features present in greater than 50% of females with Turner syndrome include short stature, low bone mineral density, learning disabilities, and delayed puberty from early ovarian failure. In particular, Turner syndrome most noticeably affects growth and endocrine health. Pediatric endocrinologists have established practice guidelines for management of Turner syndrome, including thyroid function tests starting at age 4 and evaluation for growth and pubertal development starting at age 10 [2].

For issues with growth, girls with Turner syndrome receive growth hormone therapy (GHT) injections. Without GHT, the average height of a girl with Turner syndrome is <5% by age 2 years. Thus, GHT is considered standard of care once growth failure is demonstrated and can help improve final adult height.

Due to likely ovarian failure, many girls with Turner syndrome are unable to enter puberty on their own. Estrogen replacement therapy (ERT) is often used starting at an approximate age of 12 years for girls with Turner syndrome who have not yet gone through spontaneous puberty. ERT has been successful in promoting pubertal development among girls with Turner syndrome [7]. Although ERT helps commence puberty, most girls with Turner syndrome are infertile due to ovarian failure. Regardless of karyotype, 95% of girls with Turner syndrome develop ovarian failure over time. In girls with Turner syndrome, ovarian failure may start as early as 18 weeks into fetal life. However, not every girl has complete ovarian failure at birth. The timeline and rate at which this occurs are less clear and may be different for each woman with Turner syndrome. Viable oocytes have been found in some girls with classical TS (45, X), and approximately 1–2% of women with Turner syndrome have spontaneous pregnancies [2]. While ovarian failure is a hallmark of Turner syndrome, not every girl will face infertility, and there may be time before ovarian failure occurs to preserve fertility.

Ovarian Failure in Turner Syndrome

The prevailing hypothesis for ovarian failure among those with Turner syndrome is the faulty meiotic pairing in cell division of a 45, X germ cell that leads to accelerated apoptosis of germ cells. Studies confirm that viable oocytes arise from 46, XX germ cells and 45, X germ cells are eliminated. Thus, individuals with 46, XX/45, X mosaicism in their germline theoretically have more viable oocytes than those without mosaicism. This is predicted to have direct implications on ovarian failure and thus possible fertility preservation options. While the genetic mechanism of

ovarian failure has been studied, the timeline and rate at which this occurs are less clear and may be different for each woman with Turner syndrome [8–12].

Reproductive Options

Women with Turner syndrome currently have limited reproductive options. Spontaneous pregnancy reportedly occurs in approximately 2% of women with Turner syndrome. A recent study by Bernard et al. (2016) found the spontaneous pregnancy rate may be slightly higher. Bernard et al. (2016) monitored spontaneous pregnancy rates among women with Turner syndrome and found that 5.6% (27 of 480 women) had a total of 52 spontaneous pregnancies with 30 full-term deliveries for 18 women [13]. The two predictive factors that Bernard et al. (2016) found correlated with spontaneous pregnancy occurrence were spontaneous menarche and mosaic karyotype of 45, X/46, XX. Of note, miscarriage rates were significantly greater among women with Turner syndrome than the general population, 30.8% versus 15%, respectively.

Pregnancy can be dangerous for women with Turner syndrome and heart complications. Aortic dissection, which occurs in approximately 10% of Turner syndrome pregnancies, causes maternal death in 2% of pregnant women with Turner syndrome [14, 15]. Thus, for patients with heart problems, pregnancy is not recommended. For those who become pregnant, doctors recommend surveillance for hypertension and periodic echocardiograms throughout the pregnancy.

Of note, the risk of fetal chromosome abnormalities is greater among women with Turner syndrome able to spontaneously conceive or use their own preserved oocytes compared to the general population [13]. Preimplantation genetic screening (PGS) may be utilized to screen embryos for chromosomal abnormalities prior to uterine implantation. Alternatively, women with Turner syndrome interested in carrying their own pregnancies, but unable to preserve viable oocytes or spontaneously conceive, may consider in vitro fertilization (IVF) (single-embryo transfer) pregnancies through oocyte donation. Some women elect to receive a donated oocyte from their mother or other female relative [10]. While preserving biological relatedness, this can be a socially uncomfortable option for these women. Alternatively, adoption is an option for women with Turner syndrome who are infertile or do not want to risk pregnancy or cannot afford gestational surrogacy or oocyte donation.

Turner Syndrome with Mixed Gonadal Dysgenesis (45, X/46, XY)

Individuals with Turner syndrome and presence of Y chromosome material are estimated to have a risk of 15–33% to develop gonadal tumors prior to the second decade of life [16]. However, it may be as high as 46% by the age of 50 years [17].

Nonviralized girls with normal female phenotype are at the greatest risk to develop malignancy.

Some individuals with Turner syndrome and mixed gonadal dysgenesis identify male. There appears to be an inverse correlation between testosterone production and external masculinization as well as the risk of malignancy among males with 45, X/46, XY gonadal dysgenesis. Kriplani et al. (2013) reported overall lower tumor risk among male individuals compared to those phenotypically female or with ambiguous genitalia [17]. However, males with fibrotic streak gonads are recommended to undergo gonadectomy, and males with dysgenetic gonads are recommended to have the gonads preserved in the scrotum and undergo frequent surveillance for malignancy [18].

In general, prophylactic gonadectomy is recommended for individuals with mixed gonadal dysgenesis if Y chromosome material or virilization is present due to insufficient functional ovarian tissue and the high risk of malignancy [19–22]. Fertility preservation may be possible for these individuals, dependent on the viability of gonadal tissue [23]. If doubt exists regarding gender identity, gonadectomy may be postponed until late childhood [24].

Fertility Preservation Research in Turner syndrome

Mosaicism in Turner syndrome germ cells tends to lessen the degree of ovarian failure. However, it can be difficult to know the extent of mosaicism present in the germline, as a blood karyotype does not indicate mosaicism in germ cells. In an effort to address the issue of gonadal dysgenesis in Turner syndrome, researchers have discovered that anti-Mullerian hormone (AMH) is an indicator of ovarian reserve and function [11, 12]. Girls with mosaic karyotypes more often had measurable levels of AMH, indicating that they may have viable eggs. Just 10% of girls with 45, X karyotypes had AMH levels that would suggest fertility [25]. This research has suggested that the level of mosaicism is correlated with positive fertility indicators, but further studies on ovarian failure are needed to more precisely pinpoint the age at which fertility can be best preserved among females with Turner syndrome.

Recently, oocyte cryopreservation has been pursued as a possible reproductive option for women with Turner syndrome. Case reports provide some evidence that patients with mosaic karyotypes tend to have more potentially viable eggs than those with a 45, X karyotype. A study by Oktay et al. (2010) described a 14-year-old with mosaic Turner syndrome who underwent two cycles of controlled ovarian stimulation and oocyte cryopreservation. Eleven oocytes were retrieved and cryopreserved by vitrification. The girl has not yet used the frozen oocytes to attempt a pregnancy, but the process of retrieval was successful [8]. Another recent case study involved a 16-year-old with mosaic Turner syndrome who underwent a successful laparoscopic wedge resection. Eight oocytes that matured were cryopreserved by vitrification [9]. Similar to the first case, the woman has not yet

tried to achieve a pregnancy with these retrieved oocytes. It is important to note that while oocyte cryopreservation has been successful in case reports, because this process is very new, successful pregnancy has not yet been reported [10].

Klinefelter Syndrome (47, XXY)

Incidence

Between 1 in 500 and 1 in 1000 males have Klinefelter syndrome [26]. Variants of Klinefelter syndrome, which are characterized by the presence of additional X chromosomes, occur more infrequently; approximately 1 in 50,000 or fewer newborns has a variant of Klinefelter syndrome [27].

Many affected men are diagnosed with Klinefelter syndrome as adults in the context of male infertility. As few as 10% of males with Klinefelter syndrome are diagnosed before age of 14 years. Klinefelter syndrome is underdiagnosed because the condition is often not identified in men with mild signs and symptoms. Additionally, features can vary and overlap with other conditions [26].

Klinefelter syndrome is one of the leading causes of male infertility. Approximately 3% of all infertile men have Klinefelter syndrome, and 14% of nonobstructive azoospermic men have Klinefelter syndrome [26, 28].

Natural History

Klinefelter syndrome is caused by a chromosome abnormality, which affects male physical and cognitive development. The syndrome is the result of one additional X chromosome, or a 47, XXY karyotype. The extra X chromosome interferes with male sexual development, often preventing the testes from functioning normally and reducing the levels of testosterone in the body.

Some individuals have a variant of Klinefelter syndrome—meaning they have more than one additional X chromosome, such as a 48, XXXY or 49, XXXXY karyotype. These individuals may experience more severe signs and symptoms.

Klinefelter syndrome and its variants are not inherited. Klinefelter syndrome occurs due to a sporadic event when the reproductive cells (eggs and sperm) are created. The random event is called nondisjunction, and the resulting reproductive cell has an abnormal number of chromosomes. Nondisjunction during the creation of eggs is often associated with increased maternal age [26].

The mosaic forms of Klinefelter syndrome, like 46, XY/47, XXY, are also not inherited. Mosaic Klinefelter syndrome results from a random event in cell division early in fetal development. As a result, there are two cell lines within the body. Individuals with mosaic Klinefelter may have less severe signs and symptoms.

Disease Presentation

The signs and symptoms of individuals with Klinefelter syndrome (47, XXY) and its variants tend to vary among affected individuals [27]. The following are characteristic of Klinefelter syndrome:

- Microorchidism (small testes)
- Cryptorchidism (undescended testes)
- Hypospadias (the opening of the urethra is on the underside of the penis)
- Micropenis
- Tall stature
- Learning disabilities
- Delayed speech and language development

There is also an increased risk for breast cancer and systemic lupus erythematosus among individuals with Klinefelter syndrome.

Individuals with variants of Klinefelter syndrome (more than one extra chromosome, such as 48, XXXY and 49, XXXXY) may have intellectual disabilities, distinctive facial features, skeletal abnormalities, poor coordination, and severe speech problems. As the number of extra sex chromosomes increases, so does the risk of developing these more severe health problems [27].

Effect on Fertility

Individuals with Klinefelter syndrome typically have microorchidism (small testes) and do not produce adequate levels of testosterone. Testosterone directs male sexual development before birth and during puberty. A shortage of testosterone can lead to delayed or incomplete puberty, gynecomastia, reduced facial and body hair, and infertility [27].

Infertility is typically due to severe spermatogenesis impairment responsible for azoospermia in approximately 90% of men with Klinefelter syndrome (47, XXY) and approximately 75% of men with mosaic Klinefelter syndrome [29].

Fertility Considerations

Fertility preservation may best be proposed to adolescent individuals with Klinefelter syndrome. After the onset of puberty, it is often possible to collect a semen sample for analysis. Additionally, adolescents may be able to consider alternative options to achieve fatherhood and also accept the failure of spermatozoa or immature germ cell retrieval [30]. Additionally, successful sperm retrieval may decrease with age and after testosterone therapy, further warranting fertility preservation during adolescence [28].

Y Chromosome Infertility (Contributions from Elizabeth Wignall)

Prevalence

Y chromosome infertility is also known as Y chromosome-related azoospermia. Approximately 5–15% of men with nonobstructive azoospermia and severe oligospermia have a Y chromosome microdeletion [31]. There are ethnic differences in the frequency of microdeletions affecting infertility. Japanese populations appear to have a lower frequency of AZF deletions than Caucasians [31].

Natural History

The two most common genetic factors associated with azoospermia, not caused by obstruction or other postzygotic conditions, are chromosomal abnormalities resulting in impaired testicular function and Y chromosome microdeletions leading to isolated spermatogenic impairment.

Chromosome abnormalities visible on a chromosome analysis are seen in 10–15% of men with azoospermia, 5% of men with oligospermia, and >1% of men with normspermia [32]. Microdeletions are found in 10–15% of men with azoospermia or severe oligospermia [31, 33]. These microdeletions occur in the long arm of the Y chromosome in multiple genes and are denoted as AZFa, AZFb, and AZFc. AZF stands for azoospermic factor. Deletions in these different regions have varying effect on spermatogenesis and therefore fertility [33]. The overall AZF region is essential for spermatogenesis [31].

AZF microdeletions are the result of homologous recombination in the AZF gene region [31]. The three AZF regions a, b, and c have been further delineated into five regions: AZFa, P5/proximal-P1, P5/distal-P1, P4/distal-P1, and AZFc. These deletions are the second most common genetic cause of spermatogenetic failure in infertile men and are the most common known molecular cause of infertility due to spermatogenic failure [31, 34, 35].

The most frequent deletion type is the AZFc region deletion (~80%) followed by AZFa (0.5–4%), AZFb (1–5%), and AZFbc (1–3%) deletion. Deletions which are detected as AZFabc are most likely related to abnormal karyotype such as presence of two X chromosomes and the absence of Y chromosome material in a phenotypic male (46, XX male) or the presence of a Y isochromosome (iso(Y)) [36].

Disease Presentation

Y chromosome infertility is non-syndromic. There is no outward disease presentation for Y chromosome infertility except for the sterility aspect. Unlike other conditions such as Klinefelter syndrome (46, XXY), men with microdeletions

on the Y chromosome do not have any issues with physical or psychological development [31].

Effect on Fertility

Three types of infertility can result from Y chromosome abnormalities:

- Azoospermia—a lack of sperm
- Oligospermia—moderate sperm loss
- Normspermia—normal sperm production

Deletions in AZFc result in severe oligospermia meaning sperm is produced but in minimal amounts. Men with a mutation here may still have the possibility of testicular biopsy to retrieve sperm [37].

The deficiency of AZFb function leads to an arrest in the maturation of sperm [31]. Deletions in AZFb result in azoospermia and do not result in successful testicular biopsy [37].

Deletions in AZFa also result in azoospermia and do not result in successful testicular biopsy [37]. AZFa defect results in Sertoli cell-only syndrome [31].

While deletions of the AZF region are not the only deletions on the Y chromosome that can cause infertility, they are the most well described in literature. Family planning options for individuals with AZF region deletions include ICSI from collection of ejaculate or testicular biopsy.

Additional Considerations

All male offspring of males with Y chromosome deletions will inherit the familial microdeletion. Therefore, sons born as a result of assisted reproductive technologies may also be infertile or subfertile [33, 38]. Female offspring will inherit an X chromosome from their fathers; therefore, either they or their offspring would be at increased risk for infertility.

X Chromosome Deletions and Balanced Translocations

X Chromosome Deletions in Male Infertility

While the X chromosome is enriched with genetic information associated with spermatogenesis, limited information is known about the role of X-linked genes and X chromosome copy number variants (CNV) in male infertility [39]. Evidence suggests there are copy number variants associated with spermatogenic impairment

on the X chromosome [40]. One specific copy number variant on the X chromosome, referred to as CNV67, appears to resemble the AZF regions on the Y chromosome [40]. Additional research is needed to clarify the role of the X chromosome and male fertility.

X Chromosome Deletions and Balanced Translocations in Female Infertility

Approximately 20–25% of women with primary ovarian insufficiency (POI) have an underlying genetic etiology for their fertility complications. The most common genetic cause of POI is X-chromosome abnormalities, including aneuploidies, deletions, isochromosomes, and X-autosome translocations [41, 42]. The consequence of an X-chromosome abnormality on a woman's fertility depends on the location of the abnormality and the X-chromosome inactivation pattern, also known as lyonization [43–45]. Evidence suggests the long arm, or "q" arm, of the X chromosome contains a critical region responsible for the maintenance of ovarian function and normal reproductive life span. This region is also known as the "Xq critical region" and spans Xq13 to Xq27 [45, 46]. The Xq critical region is the most common altered site on the X chromosome among individuals with POI [47].

Unbalanced chromosome translocations involving the X chromosome and autosomes are associated with additional health complications besides POI, often including intellectual disability [48, 49]. These factors should be considered when discussing the appropriateness of fertility preservation and family planning for the affected individual.

Additionally, X chromosome abnormalities may be passed on to offspring with a risk as high as 50% with each pregnancy. As certain X chromosome abnormalities are associated with disease in male offspring (and some female offspring due to skewed X-inactivation) or increased risk for miscarriage, preimplantation genetic diagnosis (PGD) and prenatal diagnostic testing should be discussed as a family planning option.

Disorders of Sexual Development

Disorders of sexual development (DSD) are conditions defined as atypical genitalia in relation to chromosomes or gonads, including ambiguous genitalia. DSDs can be broken down into several categories, including complete and partial gonadal dysgenesis, mixed gonadal dysgenesis, ovotesticular DSDs, defects with testosterone biosynthesis, androgen insensitivity syndrome, Turner syndrome, and Klinefelter syndrome. Turner syndrome, mixed gonadal dysgenesis, and Klinefelter syndrome are discussed previously in this chapter.

DSDs require special consideration of fertility preservation. Medical management of many DSDs includes gonadectomy due to an increased risk of gonadal tumor development, specifically carcinoma in situ and gonadoblastoma progressing to type 2 invasive germ cell tumors [22, 50], and lack of reliable screening methods [51]. After gonadectomy, individuals and families may consider preserving gonadal tissue for future family planning, depending on the viability of the tissue. If gonadal tissue is viable, additional consideration should be taken regarding the genetic etiology and inheritance of the DSD. There may be increased risk for chromosome abnormalities or DSDs for the children of affected individuals. The availability of preimplantation genetic screening (PGS) or diagnosis (PGD) should be discussed, as well as additional family planning options such as donor sperm/egg, surrogacy, and adoption.

Gonadal Dysgenesis

Gonadal dysgenesis is characterized as an underdevelopment of the gonadal structures due to defective migration of germ cells and/or impaired cellular organization of the fetal gonadal ridge [22, 50, 52]. The underlying etiology may be chromosomal, such as an abnormal sex chromosome structure or abnormal number of sex chromosomes, or due to a single-gene defect. The most common single-gene disorders known to result in 46, XY gonadal dysgenesis including pathogenic variants in *NR5A1, SRY, WT1,* and *SOX9* [53] Table 3.1.

Individuals with complete gonadal dysgenesis have a female phenotype. In contrast, individuals with partial gonadal dysgenesis typically have incomplete testis determination, and the external phenotype depends on the degree of testicular function. The most common karyotype among individuals with partial gonadal dysgenesis corresponds to mosaic Turner syndrome—45, X/46, XY; however, it can also be seen with other forms of Y chromosome mosaicism. For more information on gonadal dysgenesis in Turner syndrome, please refer to the Turner syndrome section of this chapter.

A conservative approach toward gonadectomy is recommended among individuals with gonadal dysgenesis. Factors, such as gonad location, internal phenotype, external phenotype, and gender of rearing, should be taken into consideration when considering gonadectomy [68]. For individuals with 46, XY partial gonadal dysgenesis raised as male, surveillance of the gonads is recommended when there are very few cases of intrascrotal malignancy reported. However, streak gonads should be removed, and dysgenic gonads should be brought to the scrotum for these individuals [68–70]. In contrast, individuals with 46, XY complete gonadal dysgenesis raised as female are at high risk for malignancy. Therefore, early bilateral gonadectomy is recommended [71–75].

Ovotesticular Disorders of Sexual Development

Individuals with ovotesticular DSDs have the presence of both ovarian and testicular tissue. External genitalia among individuals with ovotesticular DSDs are typically ambiguous. The vast majority, approximately 87%, of individuals with ovotesticular

Table 3.1 Most common single-gene disorders associated with gonadal dysgenesis

Gene	Name	Function	Associated condition(s)	Reference(s)
NR5A1	Steroidogenic factor 1 (SF1), or adrenal 4-binding protein (AD4BP)	Regulates three enzymes required for biosynthesis of corticosteroids: cholesterol side-chain cleavage enzyme (CYP11A1), steroid 210hydroxylase (CYP21A2), and the aldosterone synthase isozyme of steroid 11-beta-hydroxylase (CYP11B2)	46, XY sex reversal 3, adrenocortical insufficiency, premature ovarian failure 7, and spermatogenic failure 8	[54–59]
SRY	Sex-determining region Y or testis-determining factor	Encodes a transcription factor that binds to multiple elements within a Sox9 gonad-specific enhancer called testis-specific enhancer of Sox9 core (TESCO)	46, XX sex reversal and 46, XY sex reversal	[36, 60–62]
WT1	WT1 gene	Encodes a zinc finer DNA-binding protein that can activate or repress transcription for normal formation of the genitourinary system and mesothelial tissues	Denys–Drash syndrome, Frasier syndrome, Meacham syndrome, type 4 nephrotic syndrome, and Wilms' tumor type 1	[63, 64]
SOX9	SRY-BOX 9 or SRY-related HMG-Box Gene 9	Encodes a transcription factor essential for sex and skeletal development Expression of SRY initiates a cascade of gene interactions regulated by SOX9, which causes bipotential gonads to form into testes	Campomelic dysplasia with autosomal sex reversal, campomelic dysplasia, and acampomelic campomelic dysplasia	[65–67]

DSD have a 46, XX karyotype [76]. Approximately 50% of individuals with ovotesticular DSD have a unilateral undescended gonad, usually a testis or ovotestis. If histology is normal, fertility may be normal [74].

Gonadectomy is recommended for individuals with ovotesticular DSDs based on location of gonad, risk of malignancy, and presence of Y chromosome material [24]. For those with 46, XX ovotesticular DSD, the risk of malignancy is low [24, 50, 51, 73, 77]; therefore, gonadectomy may not be recommended or necessary. Gonadectomy decisions among these individuals should take into consideration patient and parent preferences, hormonal features, histologic features, fertility concerns, and perceived risk of tumor development [70]. In contrast, females with

presence of Y chromosome material and an intraabdominal ovotestis are recommended to undergo gonadectomy due to the lack of sufficient clinical monitoring [74, 76]. If viable tissue is removed, fertility preservation may be an option for individuals undergoing gonadectomy for ovotesticular DSD management.

Testosterone Biosynthesis Defects

There are several enzymes involved in the biosynthesis of testosterone within the body. The enzymes include StAR, P450scc, 3-Beta-HSD, 17-alpha hydroxylase, 17-20 lyase, P450 oxidoreductase, and 17-ketoreductase. Defects in the testosterone biosynthesis pathway may result in disorders of sexual development depending on the residual amount of testosterone synthesis. The overall risk of gonadal tumors among individuals with testosterone biosynthesis defects is less than 5% [78]. While male individuals with testosterone biosynthesis defects may require surgical correction of their external genitalia and/or undescended testis, gonadectomy is not typically recommended. In contrast, females with testosterone biosynthesis defects are recommended to have gonadectomy. Fertility preservation may be an option for affected females dependent on presence and viability of gonadal tissue.

StAR, or steroidogenic acute regulatory protein, mediates rapid increase in pregnenolone synthesis stimulated by tropic hormones [79]. It is required for hormone-induced steroidogenesis [80]. Biallelic pathogenic variants in the *StAR* gene result in *lipoid adrenal hyperplasia*. The pathogenic variants cause loss of steroidogenesis; subsequent cellular damage from the accumulated cholesterol esters in the adrenal cortex leads to salt wasting, hyponatremia, hypovolemia, hyperkalemia, acidosis, and death in infancy if untreated. Mineralocorticoid and glucocorticoid replacement therapy may increase life expectancy to adulthood [81].

P450scc is a cholesterol side-chain cleavage enzyme encoded by the *CYP11A1* gene. P450scc initiates steroidogenesis by converting cholesterol to pregnenolone. Specifically, P450scc catalyzes three consecutive reactions: 20-alpha-hydroxylation, 22-hydoxylation, and scission of C20,22 carbon bond [82]. Biallelic pathogenic variants in *CYP11A1* result in P450scc deficiency, also known as *adrenal insufficiency* with partial or complete 46, XY sex reversal. This disorder has a wide clinical spectrum and can present as acute adrenal insufficiency in infancy or childhood [83].

Defects in several enzymes involved in the biosynthesis of testosterone result in *congenital adrenal hyperplasia* (CAH) and its variants. CAH is an autosomal recessive inherited disorder. The majority of cases are caused by biallelic pathogenic variants in *CYP21A2*, consistent with 21-hydroxylase deficiency. Individuals with 21-hydroxylase deficiency produce too many androgens in their adrenal glands. Excess androgens result in virilization. The degree of virilization of external genitalia is dependent on the level of residual 21-hydroxylase activity. Female newborns with classic CAH typically have virilized external genitalia appearing ambiguous, while their internal genitalia and gonads are normal. In contrast, males

with classic CAH typically have normal external genitalia, but they may have small testes. Individuals with classic CAH may have the salt-wasting type or the simple virilizing type. Salt-wasting CAH causes increased loss of sodium through the urine, which can be lethal. Affected infants may present with poor feeding, weight loss, dehydration, and vomiting. Newborn screening for CAH is performed in the United States and many other countries to prevent salt-wasting crises as well as allow for appropriate medical management and gender assignment [84]. Male individuals may require surgical correction of undescended testes. Female individuals are recommended to have gonadectomy with removal of Wolffian structures and cliteroplasty. The risk to develop a gonadal tumor is reported as less than 5%. Without appropriate medical care, affected individuals are typically shorter than expected and often develop hypokalemic hypertension, hirsutism, male pattern baldness, and irregular menstruation. Early diagnosis and treatment of CAH can reduce long-term comorbidities of CAH, such as short stature, gender confusion, and psychosexual disturbance [84].

Individuals with non-classic CAH caused by 21-hydroxylase deficiency typically have normal genitalia. Affected females are often diagnosed post-puberty due to hirsutism, male pattern baldness, irregular menstrual periods, and decreased fertility. Males with non-classic CAH may have early beard growth and small testes. Individuals with mild to no symptoms may go undiagnosed.

Several variants of CAH exist, including deficiency of 17-alpha hydroxylase, 17, 20-lyase, 3-beta hydroxysteroid dehydrogenase, and combined deficiency of p450c17 and P450c21. 17-alpha-hydroxylase and 17, 20-lyase activity are regulated by 17-alpha-hydroxlase or steroid 17-alpha-monooxygenase. The gene encoding these enzymes is *CYP17*. Biallelic pathogenic variants in *CYP17* cause congenital adrenal hyperplasia due to deficiency of 17-alpha-hydroxlase. This form of CAH is characterized by ambiguous genitalia, primary amenorrhea, and male pseudohermaphroditism. Individuals may have hypertension and hypokalemic alkalosis due to excessive corticosterone and deoxycorticosterone [85, 86].

3-beta hydroxysteroid dehydrogenase is an enzyme responsible for catalyzing the oxidation and isomerization of delta-5-3-beta-hydroxysteroid precursors into delta-4-ketosteroids in the testosterone biosynthesis pathway, allowing steroid hormones to form. It is encoded by the *HSD3B2* gene [87]. Biallelic pathogenic variants in *HSD3B2* cause congenital adrenal hyperplasia (CAH) due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency. Deficiency of 3-beta-hydroxysteroid dehydrogenase results in decreased excretion of cortisol, aldosterone, progesterone, androgens, and estrogens by the adrenals and gonads. Affected individuals typically present with signs and symptoms of CAH in infancy. Males often have ambiguous genitalia, hypospadias, bifid scrotum, absent scrotum, micropenis, or a clitoris-like phallus. Females may have ambiguous genitalia. Severe deficiency of 3-beta hydroxysteroid dehydrogenase can cause salt-wasting CAH, which can be lethal if left untreated [88].

Cytochrome P450 oxidoreductase donates electrons to P450 enzymes, including the steroidogenic enzymes P450c17 and P450c21 [89]. Cytochrome P450 oxidoreductase is encoded by the *POR* gene. Biallelic pathogenic variants in *POR*

may result in a rare variant of CAH due to combined deficiency of P450c17 and P450c21 and accumulation of steroid metabolites. Affected females are typically born with ambiguous genitalia and affected males may be born under-virilized [90]. Milder pathogenic variants in *POR* may present as a more mild disorder of steroid synthesis. For example, females may present later in life with amenorrhea [91]. Biallelic pathogenic variants in *POR* may also cause Antley–Bixler syndrome with genital anomalies and disordered steroidogenesis. Antley–Bixler syndrome without genital anomalies and normal steroidogenesis is caused by pathogenic variants in a different gene, *FGFR2*. Antley–Bixler syndrome is a rare craniosynostosis syndrome characterized by radiohumeral synostosis, midface hypoplasia, choanal stenosis or atresia, joint contractures, genitourinary anomalies, and impaired steroidogenesis. As high as 80% of infants with Antley–Bixler syndrome die during the neonatal period, typically due to airway compromise [92]. Individuals with *POR* pathogenic variants may be at increased risk for adrenal insufficiency, especially during periods of illness [93].

Defects in 17-ketosteroid reductase lead to *17-beta hydroxysteroid dehydrogenase III deficiency*. This is an autosomal recessive genetic disorder that affects males (46, XY). Males with 17-beta hydroxysteroid dehydrogenase III deficiency may present at birth with female-appearing genitalia and testes in the inguinal canal, labia majora, or rarely the abdomen. The risk to develop a germ cell tumor is approximately 28% [77]. Males are recommended to have surveillance for germ cell tumors. Females are recommended to have gonadectomy prior to puberty to prevent pubertal virilization [94]. The severity of the disorder changes as individuals age due to progressive restoration of testosterone activity during adulthood. During puberty, testosterone production increases to near-normal levels, and plasma concentrations are sufficient to gradually induce marked genital virilization. Affected individuals are expected to be infertile [95] and therefore likely are not candidates for fertility preservation.

5-alpha reductase enzyme converts testosterone to dihydrotestosterone. Dihydrotestosterone is the androgen primarily responsible for virilization of male external genitalia. Individuals who are genetically male (one X chromosome and one Y chromosome) with biallelic pathogenic variants in the *SRD5A2* gene have 5-alpha reductase deficiency. Males with 5-alpha reductase deficiency have under-virilized external genitalia. The extent of the under-virilization is directly related to the level of residual enzyme activity. They may appear to have female or ambiguous external genitalia. Males are recommended to have orchiopexy and surgical correction of the external genitalia. Gonadectomy is not recommended at this time, and the risk of gonadal tumor development is unknown [50, 96]. During puberty, some secondary sexual characteristics may develop. Affected individuals with severe enzyme deficiency raised as females may be recommended to undergo prepubertal gonadectomy to prevent pubertal virilization [78]. As males with 5-alpha reductase deficiency are typically infertile, fertility preservation may not be a viable option after gonadectomy. Individuals who are genetically female (two X chromosomes) are expected to be unaffected as 5-alpha reductase activity is not necessary for development of female sex characteristics.

Androgen Insensitivity Syndrome

Androgen insensitivity syndrome (AIS) is also known as testicular feminization syndrome. It occurs in 1 out of every 20,000–64,000 individuals [77, 97]. AIS is an X-linked recessive genetic disorder caused by a pathogenic variant in the *AR*, androgen receptor, gene. Females with two X chromosomes, one containing a working copy of *AR* and the other containing a copy of *AR* with a pathogenic variant, are considered carriers of AIS. They are not expected to have signs of symptoms of AIS. Individuals with one X chromosome containing a copy of *AR* with a pathogenic variant and one Y chromosome are affected by AIS. Individuals with complete AIS cannot use androgens and are generally raised as female. They typically have completely female external genitalia, absent Mullerian structures, and gonads in the inguinal region or abdomen. Puberty is characterized by normal breast development but primary amenorrhea among these individuals.

Individuals with AIS have a low risk of gonadal tumors prepuberty (~0.8–2%); however, gonadal tumor risk increases to approximately 30% during late adulthood [50, 51, 77, 94]. By delaying gonadectomy to the late teenage years [50, 74, 97], individuals with AIS have greater average adult heights [98]and greater bone mineral density [99]. Fertility preservation may be an option with gonadectomy depending on gonadal tissue viability. However, affected females are unable to carry a pregnancy due to absence of the uterus.

Some individuals with AIS retain partial androgen receptor function. This is referred to as partial or mild AIS. These individuals may have normal female sexual development, ambiguous sexual development, or even normal male sexual development. They may be raised as female or male. Gonadectomy after puberty is also recommended for individuals with partial AIS due to increased risk of gonadal tumors [97, 99]. The risk has been reported as high as 50% among individuals with partial AIS and non-scrotal gonads [100]. Individuals with partial or mild AIS may retain fertility [101]; therefore, fertility preservation may be an option.

References

1. Stochholm K et al. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab. 2006;91(10):3897–902.
2. Pinsker JE. Clinical review: Turner syndrome: updating the paradigm of clinical care. J Clin Endocrinol Metab. 2012;97(6):E994–1003.
3. ALvarez-Nava F et al. Molecular analysis in Turner syndrome. J Pediatr. 2003;142(3):336–40.
4. Rivkees S. Beyond the karyotype: are new screening methods needed for girls with Turner's syndrome? J Pediatr Endocrinol Metab. 2006;19(9):1093–4.
5. Oliveira RM et al. Y chromosome in Turner syndrome: review of the literature. Sao Paulo Med J. 2009;127(6):373–8.
6. Sallai A et al. Y-chromosome markers in Turner syndrome: screening of 130 patients. J Endocrinol Invest. 2010;33(4):222–7.

7. Gonzalez C et al. Concise review: fertility preservation: an update. Stem Cells Transl Med. 2012;1(9):668–72.
8. Oktay K, Rodriguez-Wallberg KA, Sahin G. Fertility preservation by ovarian stimulation and oocyte cryopreservation in a 14-year-old adolescent with Turner syndrome mosaicism and impending premature ovarian failure. Fertil Steril. 2010;94(2):753 e15–9.
9. Huang JY et al. Cryopreservation of ovarian tissue and in vitro matured oocytes in a female with mosaic Turner syndrome: case report. Hum Reprod. 2008;23(2):336–9.
10. Hewitt JK et al. Fertility in Turner syndrome. Clin Endocrinol (Oxf). 2013;79(5):606–14.
11. Hagen CP et al. Serum levels of anti-Mullerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. J Clin Endocrinol Metab. 2010;95(11):5003–10.
12. Borgstrom B et al. Fertility preservation in girls with turner syndrome: prognostic signs of the presence of ovarian follicles. J Clin Endocrinol Metab. 2009;94(1):74–80.
13. Bernard V et al. Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. Hum Reprod. 2016;31(4):782–8.
14. Karnis MF et al. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. Fertil Steril. 2003;80(3):498–501.
15. Practice Committee of American Society For Reproductive Medicine. Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. Fertil Steril. 2012;97(2):282–4.
16. Verp MS, Simpson JL. Abnormal sexual differentiation and neoplasia. Cancer Genet Cytogenet. 1987;25(2):191–218.
17. Kriplani A et al. Bilateral seminomas in a 45X/46XY mosaic with Turner's phenotype: an unusual case of mixed gonadal dysgenesis. J Obstet Gynaecol Res. 2003;29(2):63–6.
18. El Moussaif N et al. 45, X/46, XY mosaicism: report of five cases and clinical review. Ann Endocrinol (Paris). 2011;72(3):239–43.
19. Mazzanti L et al. Gonadoblastoma in Turner syndrome and Y-chromosome-derived material. Am J Med Genet A. 2005;135(2):150–4.
20. Mendes JR et al. Y-chromosome identification by PCR and gonadal histopathology in Turner's syndrome without overt Y-mosaicism. Clin Endocrinol (Oxf). 1999;50(1):19–26.
21. Cools M et al. Gonadal development and tumor formation at the crossroads of male and female sex determination. Sex Dev. 2011;5(4):167–80.
22. Looijenga LH et al. Tumor risk in disorders of sex development (DSD). Best Pract Res Clin Endocrinol Metab. 2007;21(3):480–95.
23. Hovatta O. Ovarian function and in vitro fertilization (IVF) in Turner syndrome. Pediatr Endocrinol Rev. 2012;9(Suppl 2):713–7.
24. Scully RE. Gonadoblastoma; a gonadal tumor related to the dysgerminoma (seminoma) and capable of sex-hormone production. Cancer. 1953;6(3):455–63.
25. Visser JA et al. Anti-Mullerian hormone levels in girls and adolescents with Turner syndrome are related to karyotype, pubertal development and growth hormone treatment. Hum Reprod. 2013;28(7):1899–907.
26. Bojesen A, Juul S, Gravholt C. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab. 2003;88:622–6.
27. Klinefelter syndrome. 2013. [cited 20 May 2014].
28. Krausz C, Chianese C. Genetic testing and counseling for male infertility. Curr Opin Endocrinol Diabetes Obes. 2014;21(3):244–50.
29. Mau-Holzmann U. Somatic chromosomal abnormalities in infertile men and women. Cytogenet Genome Res. 2005;111:317–36.
30. Rives N et al. The feasibility of fertility preservation in adolescents with Klinefelter syndrome. Hum Reprod. 2013;28(6):1468–79.
31. Koh E et al. Azoospermia factor and male infertility. Reprod Med Biol. 2010;9(3):129–39.
32. De Braekeleer M, Dao TN. Cytogenetic studies in male infertility: a review. Hum Reprod. 1991;6(2):245–50.

33. Pryor JL et al. Microdeletions in the Y chromosome of infertile men. N Engl J Med. 1997;336(8):534–9.
34. Simoni M, Bakker E, Krausz C. EAA/EMQN best practice guidelines for molecular diagnosis of y-chromosomal microdeletions. State of the art 2004. Int J Androl. 2004;27(4):240–9.
35. Repping S et al. Recombination between palindromes P5 and P1 on the human Y chromosome causes massive deletions and spermatogenic failure. Am J Hum Genet. 2002;71(4):906–22.
36. Lange J et al. Isodicentric Y chromosomes and sex disorders as byproducts of homologous recombination that maintains palindromes. Cell. 2009;138(5):855–69.
37. Brandell RA et al. AZFb deletions predict the absence of spermatozoa with testicular sperm extraction: preliminary report of a prognostic genetic test. Hum Reprod. 1998;13(1O):2812–5.
38. Kent-First MG et al. The incidence and possible relevance of Y-linked microdeletions in babies born after intracytoplasmic sperm injection and their infertile fathers. Mol Hum Reprod. 1996;2(12):943–50.
39. Huang N et al. A screen for genomic disorders of infertility identifies MAST2 duplications associated with nonobstructive azoospermia in humans. Biol Reprod. 2015;93(3):61.
40. Lo Giacco D et al. Recurrent X chromosome-linked deletions: discovery of new genetic factors in male infertility. J Med Genet. 2014;51(5):340–4.
41. Sala C et al. Eleven X chromosome breakpoints associated with premature ovarian failure (POF) map to a 15-Mb YAC contig spanning Xq21. Genomics. 1997;40(1):123–31.
42. Sherman S. Premature ovarian failure in the fragile X syndrome. Am J Med Genet. 2000;97:189–94.
43. Kalz-Fuller B et al. Characterisation, phenotypic manifestations and X-inactivation pattern in 14 patients with X-autosome translocations. Clin Genet. 1999;55(5):362–6.
44. Schmidt M, Sart DD. Functional disomies of the X chromosome influence the cell selection and hence the X inactivation pattern in females with balanced X-autosome translocations: a review of 122 cases. Am J Med Genet. 1992;42(2):161–9.
45. Therman E, Laxova R, Susman B. The critical region on the human Xq. Hum Genet. 1990;85(5):455–61.
46. Sarto GE, Therman E, Patau K. X inactivation in man: a woman with t(Xq--;12q+). Am J Hum Genet. 1973;25(3):262–70.
47. Moyses-Oliveira M et al. Genetic mechanisms leading to primary amenorrhea in balanced X-autosome translocations. Fertil Steril. 2015;103(5):1289–96. e2
48. Chen CP et al. Primary ovarian failure in a mentally retarded woman with a de novo unbalanced X;autosome translocation. Fertil Steril. 2006;86(5):1514 e1–2.
49. Chen CP et al. Array CGH characterization of an unbalanced X-autosome translocation associated with Xq27.2-qter deletion, 11q24.3-qter duplication and Xq22.3-q27.1 duplication in a girl with primary amenorrhea and mental retardation. Gene. 2014;535(1):88–92.
50. Pleskacova J et al. Tumor risk in disorders of sex development. Sex Dev. 2010;4(4–5):259–69.
51. Deans R et al. Timing of gonadectomy in adult women with complete androgen insensitivity syndrome (CAIS): patient preferences and clinical evidence. Clin Endocrinol (Oxf). 2012;76(6):894–8.
52. MacLaughlin DT, Donahoe PK. Sex determination and differentiation. N Engl J Med. 2004;350(4):367–78.
53. Douglas G et al. Consensus in guidelines for evaluation of DSD by the texas children's hospital multidisciplinary gender medicine team. Int J Pediatr Endocrinol. 2010;2010:919707.
54. Luo X, Ikeda Y, Parker KL. A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation. Cell. 1994;77(4):481–90.
55. Biason-Lauber A, Schoenle EJ. Apparently normal ovarian differentiation in a prepubertal girl with transcriptionally inactive steroidogenic factor 1 (NR5A1/SF-1) and adrenocortical insufficiency. Am J Hum Genet. 2000;67(6):1563–8.

56. Achermann JC et al. A mutation in the gene encoding steroidogenic factor-1 causes XY sex reversal and adrenal failure in humans. Nat Genet. 1999;22(2):125–6.
57. Correa RV et al. A microdeletion in the ligand binding domain of human steroidogenic factor 1 causes XY sex reversal without adrenal insufficiency. J Clin Endocrinol Metab. 2004;89(4):1767–72.
58. Lourenco D et al. Mutations in NR5A1 associated with ovarian insufficiency. N Engl J Med. 2009;360(12):1200–10.
59. Bashamboo A et al. Human male infertility associated with mutations in NR5A1 encoding steroidogenic factor 1. Am J Hum Genet. 2010;87(4):505–12.
60. Sekido R, Lovell-Badge R. Sex determination involves synergistic action of SRY and SF1 on a specific Sox9 enhancer. Nature. 2008;453(7197):930–4.
61. Cameron FJ, Sinclair AH. Mutations in SRY and SOX9: testis-determining genes. Hum Mutat. 1997;9(5):388–95.
62. Harley VR et al. Defective importin beta recognition and nuclear import of the sex-determining factor SRY are associated with XY sex-reversing mutations. Proc Natl Acad Sci U S A. 2003;100(12):7045–50.
63. Hossain A, Saunders GF. The human sex-determining gene SRY is a direct target of WT1. J Biol Chem. 2001;276(20):16817–23.
64. Wagner KD et al. The Wilms' tumor suppressor Wt1 encodes a transcriptional activator of the class IV POU-domain factor Pou4f2 (Brn-3b). Gene. 2003;305(2):217–23.
65. Cox JJ et al. A SOX9 duplication and familial 46, XX developmental testicular disorder. N Engl J Med. 2011;364(1):91–3.
66. Qin Y, Bishop CE. Sox9 is sufficient for functional testis development producing fertile male mice in the absence of Sry. Hum Mol Genet. 2005;14(9):1221–9.
67. Wagner T et al. Autosomal sex reversal and campomelic dysplasia are caused by mutations in and around the SRY-related gene SOX9. Cell. 1994;79(6):1111–20.
68. McCann-Crosby B et al. State of the art review in gonadal dysgenesis: challenges in diagnosis and management. Int J Pediatr Endocrinol. 2014;2014(1):4.
69. Martinerie L et al. Impaired puberty, fertility, and final stature in 45, X/46, XY mixed gonadal dysgenetic patients raised as boys. Eur J Endocrinol. 2012;166(4):687–94.
70. Cools M et al. Managing the risk of germ cell tumourigenesis in disorders of sex development patients. Endocr Dev. 2014;27:185–96.
71. Gourlay WA et al. Gonadal tumors in disorders of sexual differentiation. Urology. 1994;43(4):537–40.
72. Rocha VB et al. Complete gonadal dysgenesis in clinical practice: the 46, XY karyotype accounts for more than one third of cases. Fertil Steril. 2011;96(6):1431–4.
73. Dumic M et al. Bilateral gonadoblastoma in a 9-month-old infant with 46, XY gonadal dysgenesis. J Endocrinol Invest. 1993;16(4):291–3.
74. Fallat ME, Donahoe PK. Intersex genetic anomalies with malignant potential. Curr Opin Pediatr. 2006;18(3):305–11.
75. Michala L et al. Swyer syndrome: presentation and outcomes. BJOG. 2008;115(6):737–41.
76. Wiersma R. The clinical spectrum and treatment of ovotesticular disorder of sexual development. Adv Exp Med Biol. 2011;707:101–3.
77. Hughes IA et al. Consensus statement on management of intersex disorders. J Pediatr Urol. 2006;2(3):148–62.
78. Abaci A, Catli G, Berberoglu M. Gonadal malignancy risk and prophylactic gonadectomy in disorders of sexual development. J Pediatr Endocrinol Metab. 2015;28(9–10):1019–27.
79. Sugawara T et al. Human steroidogenic acute regulatory protein: functional activity in COS-1 cells, tissue-specific expression, and mapping of the structural gene to 8p11.2 and a pseudogene to chromosome 13. Proc Natl Acad Sci U S A. 1995;92(11):4778–82.
80. Clark BJ et al. The purification, cloning, and expression of a novel luteinizing hormone-induced mitochondrial protein in MA-10 mouse Leydig tumor cells. characterization of the steroidogenic acute regulatory protein (StAR). J Biol Chem. 1994;269(45):28314–22.

81. Bose HS et al. The pathophysiology and genetics of congenital lipoid adrenal hyperplasia. N Engl J Med. 1996;335(25):1870–8.
82. Sahakitrungruang T et al. Partial defect in the cholesterol side-chain cleavage enzyme P450scc (CYP11A1) resembling nonclassic congenital lipoid adrenal hyperplasia. J Clin Endocrinol Metab. 2011;96(3):792–8.
83. Kim CJ et al. Severe combined adrenal and gonadal deficiency caused by novel mutations in the cholesterol side chain cleavage enzyme, P450scc. J Clin Endocrinol Metab. 2008;93(3):696–702.
84. Choi JH, Kim GH, Yoo HW. Recent advances in biochemical and molecular analysis of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Ann Pediatr Endocrinol Metab. 2016;21(1):1–6.
85. Biglieri EG. 17 alpha-Hydroxylase deficiency: 1963–1966. J Clin Endocrinol Metab. 1997;82(1):48–50.
86. Martin RM et al. P450c17 deficiency in Brazilian patients: biochemical diagnosis through progesterone levels confirmed by CYP17 genotyping. J Clin Endocrinol Metab. 2003;88(12):5739–46.
87. Rheaume E et al. Structure and expression of a new complementary DNA encoding the almost exclusive 3 beta-hydroxysteroid dehydrogenase/delta 5-delta 4-isomerase in human adrenals and gonads. Mol Endocrinol. 1991;5(8):1147–57.
88. Rheaume E et al. Congenital adrenal hyperplasia due to point mutations in the type II 3 beta-hydroxysteroid dehydrogenase gene. Nat Genet. 1992;1(4):239–45.
89. Miller WL. Congenital adrenal hyperplasia. N Engl J Med. 1986;314(20):1321–2.
90. Peterson RE et al. Male pseudohermaphroditism due to multiple defects in steroid-biosynthetic microsomal mixed-function oxidases. A new variant of congenital adrenal hyperplasia. N Engl J Med. 1985;313(19):1182–91.
91. Fluck CE et al. Mutant P450 oxidoreductase causes disordered steroidogenesis with and without Antley-Bixler syndrome. Nat Genet. 2004;36(3):228–30.
92. McGlaughlin KL et al. Spectrum of Antley-Bixler syndrome. J Craniofac Surg. 2010;21(5):1560–4.
93. Reardon W et al. Evidence for digenic inheritance in some cases of Antley-Bixler syndrome? J Med Genet. 2000;37(1):26–32.
94. George MM et al. The clinical and molecular heterogeneity of 17betaHSD-3 enzyme deficiency. Horm Res Paediatr. 2010;74(4):229–40.
95. Eckstein B et al. The nature of the defect in familial male pseudohermaphroditism in Arabs of Gaza. J Clin Endocrinol Metab. 1989;68(2):477–85.
96. Okeigwe I, Kuohung W. 5-Alpha reductase deficiency: a 40-year retrospective review. Curr Opin Endocrinol Diabetes Obes. 2014;21(6):483–7.
97. Mendoza N, Motos MA. Androgen insensitivity syndrome. Gynecol Endocrinol. 2013;29(1):1–5.
98. Han TS et al. Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. Eur J Endocrinol. 2008;159(2):179–85.
99. Bertelloni S, Baroncelli GI, Mora S. Bone health in disorders of sex differentiation. Sex Dev. 2010;4(4–5):270–84.
100. Olsen MM et al. Gonadoblastoma in infancy: indications for early gonadectomy in 46XY gonadal dysgenesis. J Pediatr Surg. 1988;23(3):270–1.
101. Petroli RJ et al. Preserved fertility in a patient with gynecomastia associated with the p.Pro695Ser mutation in the androgen receptor. Sex Dev. 2014;8(6):350–5.

Chapter 4
Malignant Hematologic Diseases

Introduction

The overall survival and cure rates of patients with hematologic malignancies (HMs) have improved dramatically during the last decades after the introduction of allogeneic hematopoietic stem cell transplantation (HSCT) and modern antitumor therapy modalities [1].

Many women of fertile age can therefore expect to survive. The loss of fertility is a common result of treatment affecting quality of life (QoL) in cancer survivors, and parenthood is an important quality of life aspect for this group [1]. As a consequence, fertility issues and fertility preservation are important issues to address for healthcare professionals dealing with cancer patients [1].

Leukemia

Definition

Leukemia is cancer of the blood cells. Most blood cells form in the bone marrow. In leukemia, immature blood do not work the way they should, and they crowd out the healthy blood cells in the bone marrow [2].

White blood cells are the most common type of blood cell to become cancer. But red blood cells and platelets may also become cancer.

Leukemia can be either acute or chronic.

Acute leukemia is a fast-growing cancer that usually gets worse quickly.

Chronic leukemia is a slower-growing cancer that gets worse slowly over time.

Treatment and prognosis for leukemia depend on the type of blood cell affected and whether the leukemia is acute or chronic [2].

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_4

Incidence and Epidemiology

Leukemia is the second most common blood cancer after lymphoma and includes several diseases. It occurs most often in older adults; however, it is one of the most common childhood cancers [2].

Different types of leukemia depend on the type of blood cell that becomes cancer. Major types of leukemia:

- Acute lymphocytic leukemia (ALL).
- Chronic lymphocytic leukemia (CLL).
- Acute myelogenous leukemia (AML).
- Chronic myelogenous leukemia (CML), NCI.
- The most common types of leukemia in adults are AML and CLL, followed by ALL and CML.

The overall incidence rates for leukemia have increased on average 0.2% each year from 2002 to 2011, while overall mortality rates have fallen an average of 1% each year from 2001 to 2010 [2].

Incidence and mortality rates are higher in whites than in people of other racial and ethnic groups. And it is slightly more common in men than women [2].

Risk Factors

General risk factors for leukemia:

- Being male
- Smoking
- Exposure to certain chemicals such as benzene
- Exposure to radiation
- Past treatment with chemotherapy or radiation therapy
- Having certain genetic disorders
- Having certain blood disorders
- Having a family history of leukemia

There are no standard screening tests for leukemia.
Depending on the type of leukemia, *standard treatments* include:

- Watchful waiting
- Chemotherapy
- Targeted therapy
- Radiation therapy
- Stem cell transplant [2]

Malignant Myeloid Diseases

Acute Myelogenous Leukemia (AML)

Definition

AML is the result of a sequence of somatic mutations in a multipotential primitive hematopoietic cell or, in some cases, a more differentiated progenitor cell [3].

Incidence

Acute myeloid leukemia (AML) has 5-year survival rates of 24% overall and 60% in children under 15 years of age [4].

Physiopathology

The mutant hematopoietic cell gains a growth and/or survival advantage in relationship to the normal pool of stem cells. As the progeny of this mutant, now leukemic, multipotential cell proliferates to form approximately 11 billion or more cells, normal hematopoiesis is inhibited, and normal red cell, neutrophil, and platelet blood levels fall [3].

Risk Factors

- Exposure to radiation.
- Chronic exposure to high doses of benzene.
- Chronic, heavy inhalation of tobacco smoke increases the incidence of the disease.
- A proportion of cases develop after a patient being exposed to intensive chemotherapy, especially with alkylating agents or topoisomerase II inhibitors [3].

Clinical Manifestations

- Anemia leads to weakness, exceptional limitations, and pallor.
- Thrombocytopenia leads to spontaneous hemorrhage, usually in the skin.
- Neutropenia and monocytopenia lead to poor wound healing and minor infections. Severe infection usually does not occur at diagnosis but will if the disease progresses because of lack of treatment or if chemotherapy intensifies the decrease of blood neutrophil and monocyte levels.

Diagnosis

The diagnosis is made by:

- Measurement of blood cell counts
- Examination of blood and marrow cells: identification of leukemic blast cells in the marrow and blood

The diagnosis of AML specifically is confirmed by identification of myeloperoxidase activity in blast cells or by identifying characteristic cluster of differentiation (CD) antigens on the blast cells (e.g., CD13, CD33).

The leukemic stem cell is capable of imperfect differentiation and maturation [3].

Treatment

In AML, regimens devoid of alkylating agents are most commonly used. AML usually is treated with cytarabine and an anthracycline antibiotic, although other drugs may be added or substituted in poor-prognosis, refractory, or relapsed patients.

High-dose chemotherapy and either autologous stem cell infusion or allogeneic stem cell transplantation may be used in an effort to treat relapse or patients at high risk to relapse after chemotherapy treatment.

The probability of remission ranges from approximately 80% in children to less than 25% in octogenarians. The probability for cure decreases from approximately 50% in children to virtually zero in octogenarians [3].

In AML, regimens without alkylating agents are most commonly used, and thus infertility may be even less common than in ALL [4]. Although less extensively documented, fertility preservation issues in AML are probably comparable to those in women with ALL [5].

Chronic Myelogenous Leukemia (CML)

Definition

CML is a pluripotential stem cell disease; the hematopoietic cells contain a reciprocal translocation between chromosomes 9 and 22 in more than 95% of patients, referred to as the *Philadelphia (Ph) chromosome*, which is identified by molecular diagnostic analysis [6].

CMLs include:

- BCR rearrangement-positive CML
- Chronic myelomonocytic leukemia
- Juvenile myelomonocytic leukemia
- Chronic neutrophilic leukemia

- Chronic eosinophilic leukemia
- Chronic basophilic leukemia

Epidemiology

CML accounts for approximately 15% of all cases of leukemia or approximately 5000 new cases per year in the United States. The incidence in the United States is approximately 2.0 per 100,000 persons for men and approximately 1.1 per 100,000 persons for women. The incidence around the world varies.

The age-specific incidence rate for CML in the United States increases logarithmically with age, from approximately 0.2 per 100,000 persons younger than 20 years to a rate of approximately 10.0 per 100,000 octogenarians per year.

Although CML occurs in children and adolescents, less than 10% of all cases occur in patients between 1 and 20 years old. CML represents approximately 3% of all childhood leukemias [3].

Natural History

The natural history of the disease is to undergo clonal evolution into an accelerated phase and/or a rapidly progressive phase resembling acute leukemia, which is refractory to therapy. The chronic phase usually is followed by an accelerated phase that often terminates in acute leukemia (blast crisis), at which point therapy with imatinib mesylate and other agents may induce a remission in a proportion of patients, but median survival is measured in months. Blast crisis results in a myelogenous leukemic phenotype in 75% of cases and a lymphoblastic leukemic phenotype in approximately 25% of cases [2, 3].

Clinical Manifestations

70% of patients are symptomatic at diagnosis; the symptoms are vague, nonspecific, and gradual in onset (weeks to months).

Most frequent symptoms include:

- Easy fatigability
- Loss of sense of well-being
- Decreased tolerance to exertion
- Anorexia
- Abdominal discomfort: related to splenic enlargement
- Weight loss
- Excessive sweating [4, 6]

A physical examination may detect pallor and splenomegaly [4], and sternal tenderness, especially the lower portion, is common; occasionally, patients notice it themselves [6].

Laboratory Findings

- Anemia
- Extreme granulocytosis and granulocytic immaturity
- Large proportion of myelocytes and mature neutrophils, absolute basophilia
- Normal or elevated platelet counts

Bone Marrow Morphology

The marrow is markedly hypercellular, and hematopoietic tissue takes up 75–90% of the marrow volume, with fat markedly reduced [4]. Granulopoiesis is dominant, with a granulocytic-to-erythroid ratio between 10:1 and 30:1, rather than the normal 2:1 to 4:1.

Marrow cells contain the Philadelphia (Ph) chromosome in approximately 90% of cases by cytogenetic analysis [6].

Treatment

Nowadays, CML is treated with *imatinib mesylate (imatinib)* which is a specific tyrosine kinase inhibitor and is now used as initial therapy in almost all patients with CML presenting in the chronic phase. Disease usually responds to imatinib mesylate, and median survival has been extended significantly.

In cases where the white cell count is markedly elevated, *hydroxyurea* can be used prior to or in conjunction with imatinib.

Allogeneic stem cell transplantation can cure the disease, especially if the transplantation is applied early in the chronic phase; HSCT is used in case of failure of drug treatment [5].

Effect on Fertility

Imatinib is not thought to impair fertility in women [4]. To date, there is insufficient data on the effects of second-generation tyrosine kinase inhibitors on reproductive function, although successful pregnancies have been reported after use of these drugs [4–6] .

Fertility Preservation Options

Fertility preservation methods should be applied in case of HSCT [5].

As in acute leukemia cases, ovarian tissue may be infiltrated by the disease [4]. As the presence of the BCR–ABL gene is a characteristic of the disease, molecular detection of leukemic cells in ovarian tissue can always be carried out [5].

Moreover, patients with CML, especially those treated with total body irradiation (TBI) followed by BMT, may be at unique risk of relapse with subsequent pregnancy [7]. Indeed, the immunological surveillance required to sustain remission after BMT might be compromised by the immunotolerant state of pregnancy, contributing to this increased risk of relapse.

It is important to note that patients who show a positive response to imatinib are advised not to interrupt their therapy, because of the risk of relapse and progression [5].

A patient on Gleevec should only try to conceive if the oncologist allows her to stop the medication during pregnancy. Very close monitoring by oncologists, as well as obstetricians, should however be recommended. Although the experience is limited, several successful pregnancies and deliveries have been reported in patients on Gleevec [5].

Oocytes of cancer patients stored over the long term can successfully develop to the in vitro cleavage stage and result in a live birth. This example of a successful pregnancy via oocyte banking should be a positive sign of hope for patients subjected to cancer treatments with potential risk of infertility. [4]

Malignant Lymphoid Diseases

Acute Lymphoblastic Leukemia (ALL)

Definition

ALL is a neoplastic disease that results from multistep somatic mutations in a single lymphoid progenitor cell at one of several discrete stages of development.

Childhood ALL originates in the T and B lymphoblasts in the bone marrow.

Leukemic cells divide more slowly and require more time to synthesize DNA than normal hematopoietic counterparts [8]. However, leukemic cells accumulate relentlessly because of their altered response to growth and death signals [9]. They compete successfully with normal hematopoietic cells, resulting in anemia, thrombocytopenia, and neutropenia. At diagnosis, leukemic cells not only have replaced normal marrow cells but also have disseminated to various extramedullary sites [10].

Etiology

Environmental agents, such as ionizing radiation and chemical mutagens, have been implicated in the induction of ALL in some patients. However, in most cases, no etiologic factors are discernible.

Incidence

The age-adjusted incidence rate of ALL was 1.6 per 100,000 men and women per year in the United States, based on cases diagnosed in 2001–2005 from 17 Surveillance, Epidemiology, and End Results (SEER) geographic areas [10].

The median age at diagnosis for ALL is 13 years, and approximately 61% are diagnosed before the age of 20 years. ALL is the most common malignancy diagnosed in patients younger than age 15 years, accounting for 23% of all cancers and 76% of all leukemias in this age group. Only 20% of adult acute leukemias are ALL [10].

Since 1975, there has been a gradual increase in the incidence of ALL [11]. A sharp peak in ALL incidence is observed among children aged 2–3 years (>90 cases per 1 million per year), with rates decreasing to fewer than 30 cases per 1 million by age 8 years [8]. It is the most common childhood cancer, accounts for approximately 75% of all childhood leukemias [2]. Indeed, 75% of ALL cases occur in children [8]. In the United States, ALL occurs at an annual rate of approximately 41 cases per 1 million people aged from 0 to 14 years and approximately 17 cases per 1 million people aged 15–19 years [11]. There are approximately 3100 children and adolescents younger than 20 years diagnosed with ALL each year in the United States. The incidence of ALL appears to be highest in Hispanic children (43 cases per 1 million) [8] and in white children compared to black [8]. Five-year ALL survival rates are 66.4% overall and 90% in children under 15 years of age [10].

Clinical Manifestations

Early signs and symptoms may be like the flu or other common diseases:

- Weakness, fatigue, and lethargy
- Fever or night sweats
- Easy bruising or bleeding
- Petechiae (flat, pinpoint spots under the skin, caused by bleeding)
- Shortness of breath
- Weight loss or loss of appetite
- Pain in the bones

More than 25% of patients, especially young children, may have a limp, bone pain, arthralgia, or an unwillingness to walk because of leukemic infiltration of the periosteum, bone, or joint or because of expansion of the marrow cavity by leukemic cells.

- Pain or feeling of fullness below the ribs
- Painless lumps in the neck, underarm, stomach, or groin
- Infections

Physical Findings

- Pallor, petechiae, and ecchymosis in the skin and mucous membranes.
- Bone tenderness as a result of leukemic infiltration or hemorrhage that stretches the periosteum.

- Liver, spleen, and lymph nodes are the most common sites of extramedullary involvement, and the degree of organomegaly is more pronounced in children than in adults.
- An anterior mediastinal (thymic) mass is present in 8 to 10% of childhood cases and in 15% of adult cases.
- A bulky, anterior mediastinal mass can compress the great vessels and trachea and possibly lead to the superior vena cava syndrome or the superior mediastinal syndrome.

Laboratory Findings

Common findings in patients with newly diagnosed ALL:

- Approximately 90% of the patients have circulating leukemic blast cells at diagnosis.
- Hyperleukocytosis (>100 × 109 white cells/L) occurs in 11–13% of white children but occurs more often in black children (23%) and adults (16%) because they are more likely to have T-cell ALL.
- Anemia.
- Neutropenia: profound neutropenia (<0.5 × 109/L) is found in 20–40% of patients, rendering them at high risk for infection.
- Thrombocytopenia.

The severity of these findings reflects the degree of marrow replacement by leukemic lymphoblasts.

ALL has many subtypes and can be classified by immunologic, cytogenetic, and molecular genetic methods.

Marrow involvement of ALL as seen by light microscopy is defined as follows:

- M1: fewer than 5% blast cells
- M2: 5–25% blast cells
- M3: greater than 25% blast cells

Almost all patients with ALL present with an M3 marrow.

Prognostic

Among children with ALL, approximately 98% attain remission, and approximately 85% of patients aged 1–18 years with newly diagnosed ALL treated on current regimens are expected to be long-term event-free survivors, with over 90% surviving at 5 years [12].

Risk Factors

Few factors associated with an increased risk of ALL have been identified:

- Prenatal exposure to X-rays

- Postnatal exposure to high doses of radiation (e.g., therapeutic radiation as previously used for conditions such as tinea capitis and thymus enlargement)
- Genetic conditions that include the following:
  - Down syndrome
  - Neurofibromatosis (*NF1*)
  - Bloom syndrome (*BLM*)
  - Fanconi anemia (multiple genes; ALL is observed much less frequently than acute myeloid leukemia [AML])
  - Ataxia telangiectasia (*ATM*)
  - Li–Fraumeni syndrome (*TP53*)

Treatment

Supportive care for optimal management of ALL:

- Immediate treatment or prevention of metabolic and infectious complications.
- Rational use of blood products.
- Amelioration of nausea and vomiting.
- Pain control.
- Continuous psychosocial support for the patient and family is essential.

The most effective contemporary treatment regimens for *B-cell* ALL are drug combinations that include:

- Cyclophosphamide given over a relatively short time (3–6 months).
- Rituximab (anti-CD20) has been incorporated in front-line clinical trials for adults with B-cell ALL, yielding promising results [10, 13, 14].

Precursor B-Cell and T-Cell ALL

Treatment for leukemias affecting the precursor B-cell and T-cell lineages consists of three standard phases:

- Remission: the first goal of therapy for patients with leukemia is inducing a complete remission and restoring normal hematopoiesis.
- Induction: the induction regimen typically includes glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and l-asparaginase for children or an anthracycline for adults [10, 15, 16].
- Intensification (consolidation) and prolonged continuation therapy.

Children with high- or very-high-risk ALL, and nearly all young adults with ALL, receive four or more drugs during remission induction in contemporary clinical trials.

Nearly 90% of children and 40% of adults can expect long-term, leukemia-free survival—and probable cure—with contemporary treatment [10].

Effect on Fertility

The rate of treatment-induced infertility in leukemia patients depends on whether HSCT, with its highly gonadotoxic conditioning regimens, is undertaken [17].

Contemporary treatment protocols for ALL use lower doses of gonadotoxic agents, particularly cyclophosphamide, and are thus unlikely to cause infertility [18]. Thus, fertility preservation options should be reserved mainly for patients undergoing HSCT.

Fertility Preservation Options

As most ALL cases occur in children, ovarian tissue cryopreservation is the best option to preserve fertility, possibly associated with oocyte aspiration at the time of ovarian harvesting, in vitro maturation, and cryopreservation by vitrification.

However, ovarian reimplantation carries a high risk of reintroducing leukemic cells. Indeed, PCR methods and xenografting to nude mice using ovarian biopsies from women with ALL showed leukemia cells in 70% of cases [19]. Not all cases of ALL display genetic markers, and, so far, there are no sensitive molecular methods to evaluate the risk of contamination by malignant cells.

Women suffering from ALL or parents of girls with the disease should be clearly informed that any harvested tissue will only be able to be used in the future for IVM or reimplantation of isolated follicles.

Postponing cryopreservation until after induction chemotherapy might be an option to eradicate leukemic cells from biopsies, but one cycle of chemotherapy is not sufficient to purge the ovary of malignant cells [19, 20], while it may already be deleterious to oocyte quality [21, 22].

In older women with leukemia, oocyte or embryo cryopreservation may be impossible, as treatment should usually not be delayed for more than 1 week.

Chronic Lymphocytic Leukemia (CLL)

Definition

CLL is a neoplastic disease characterized by the accumulation of monoclonal population of small, mature-appearing lymphocytes in the blood, marrow, and lymphoid tissues [23].

Etiology

The causes of this disease are unknown; although genetic factors have been found to play a role, no single environmental risk factor has been found to be predictive for CLL [23]. Hereditary factors: although most cases of CLL are sporadic, multiple cases of leukemia may be found within a single family.

Epidemiology

CLL has an average incidence of 2.7 persons per 100,000 in the United States. Its incidence ranges from <1 to 5.5 per 100,000 people worldwide [24]. The risk of developing CLL increases progressively with age and is 2.8 times higher for older men than for older women [25]. At diagnosis, most patients are older than 60 years of age, and 90% are older than age 50 years [24]. The median age of onset is approximately 67 years. The disease is rare in persons younger than 25 years of age. There is a 2:1 male-to-female incidence and prevalence of CLL.

Clinical Manifestations

There is a wide variation in the rate of clinical progression. Many patients (more than 25%) are asymptomatic at the time of diagnosis and are observed without treatment until they develop symptoms or evidence of disease progression.

Disease Presentation

- Asymptomatic patients
- Nontender lymphadenopathy

Nearly 80% of all CLL patients have nontender lymphadenopathy at diagnosis, most commonly involving the cervical, supraclavicular, or axillary lymph nodes. Lymph node enlargement can range from being minimal to massive, the latter potentially causing local disfiguration or organ dysfunction. Some patients may develop symptoms of upper airway obstruction because of oral–pharyngeal lymphadenopathy.

- Approximately half of all CLL patients present with mild to moderate splenomegaly.
- Unexplained absolute lymphocytosis.
- Reduced exercise tolerance, fatigue, or malaise: patients may experience such symptoms even when they apparently lack major organ involvement or anemia.
- Exacerbation of another underlying medical condition, such as pulmonary, cerebrovascular, or coronary artery disease.
- Chronic rhinitis secondary to nasal involvement of CLL cells [23].

Signs and symptoms of advanced disease:

- Weight loss.
- Recurrent infections.
- Bleeding secondary to thrombocytopenia.
- Symptomatic anemia.
- Night sweats and fevers (the so-called B symptoms) are uncommon and should prompt evaluation for complicating infectious disease.

- Patients with CLL are more prone to viral or bacterial infections secondary to impaired T-cell immunity or hypogammaglobulinemia, respectively.

Patients with CLL are prone to developing systemic autoimmune disease. The most common autoimmune disorders result from autoantibodies that are directed against hematopoietic cell antigens, such as those found on red blood cells or platelets, although other types of autoimmune disorder also appear more common among CLL patients than in the general population [23].

Laboratory Features

- The diagnosis of CLL requires a sustained *monoclonal lymphocytosis* greater than 5000/μL (5×10^9/L). At diagnosis, the absolute lymphocyte count generally exceeds 10,000/μL (10×10^9/L) and is sometimes greater than 100,000/μL (100×10^9/L). Morphologically, the leukemic cells are phenocopies of normal blood small lymphocytes.
- Patients with CLL may develop anemia secondary to leukemic marrow infiltration, the myelosuppressive effect of chemotherapy and inhibiting cytokines, autoimmunity directed against red cell antigens, hypersplenism, and/or a poor nutritional status that leads to deficiency of folic acid, vitamin B_{12}, or iron.
- Marrow findings: the marrow invariably is infiltrated with leukemic lymphocytes.

Treatment

Newly diagnosed patients with asymptomatic early-stage disease should be monitored without therapy unless they have evidence of progressive disease.

Therapeutic agents:

- Deoxyadenosine analogues, such as fludarabine.
- Alkylating agents, such as bendamustine and chlorambucil (useful in the palliative therapy of patients with advanced-stage disease, it does not appear to improve survival), and monoclonal antibodies, notably alemtuzumab and rituximab, alone or in combination with purine analogues, alkylating agents, or glucocorticoids, have improved treatment response rates.
- Nonmyeloablative hematopoietic stem cell transplantation can be used selectively for some patients.
- Experimental immune-gene therapy may be available in the future.
- Splenectomy: it may ameliorate the cytopenias associated with advanced-stage CLL, particularly thrombocytopenia [23, 26, 27].
- Radiation therapy: irradiation remains a useful technique for localized treatment to ameliorate symptoms caused by nerve impingement, vital organ compromise, painful bone lesions, or bulky disfigurement.

Effect on Fertility

Effect on fertility is related to treatment.

This disease is extremely rare in younger patients.

Lymphoma

Incidence and Mortality

Lymphoma, including Hodgkin lymphoma and non-Hodgkin lymphoma (NHL), is the most common blood cancer in the United States and is estimated to represent approximately 5% of all new cancers diagnosed in the United States in 2014 [28].

Because of improvements in treatment, the mortality rate for Hodgkin lymphoma has decreased by nearly 70% since 1975, even though the incidence rate has remained stable. Incidence rates for Hodgkin lymphoma are highest for whites and African Americans; mortality rates are highest for whites, Hispanics, and African Americans [28].

Risk factors for both Hodgkin lymphoma and NHL include:

- Being male
- Weakened immune system
- Human immunodeficiency virus (HIV) or Epstein–Barr virus infection
- *Helicobacter pylori* infection

Treatment

Standard treatments for both types of lymphoma are chemotherapy, radiation therapy, and stem cell transplant.

Hodgkin Lymphoma

Definition

Classic Hodgkin lymphoma (HL) is a neoplasm of lymphoid tissue, in most cases derived from germinal center B cells, defined by the presence of the malignant Hodgkin and Reed–Sternberg cells with a characteristic immunophenotype and appropriate cellular background [29].

Hodgkin lymphoma contains four histologic subtypes distinguished on the basis of microscopic appearance and relative proportions of Hodgkin/Reed–Sternberg cells, lymphocytes, and fibrosis:

- Nodular sclerosis
- Mixed cellularity
- Lymphocyte rich
- Lymphocyte depleted

Incidence

Risk of Hodgkin lymphoma is higher in both early adulthood and later life with a bimodal incidence with peaks at ages 15 to 34 and in those older than age 60 years [30, 31] with a median age of onset of 38 years [29].

Three distinct forms of Hodgkin lymphoma:

- Childhood form (ages 0–14 years) (rare)
- Young adult form (15–34 years)
- Older adult form (55–74 years)

Prognosis

Overall 5-year survival rates of 87% and even 96% in women under 20 years of age [5]. Prognoses are promising, with 87% of cases surviving 5 years post-diagnosis [32].

Clinical Manifestations

Symptomatic "B" disease: constitutional symptoms that are indicative of bad prognosis.

- Fever in excess of 38 °C
- Drenching night sweats
- Weight loss exceeding 10% of baseline body weight during the 6-month preceding diagnosis

Signs and symptoms not prognostically significant:

- Fevers are usually of low grade and irregular.
- Cyclic pattern of high fevers for 1–2 weeks alternating with afebrile periods of similar duration is present at diagnosis. This latter classic Pel–Ebstein fever is virtually diagnostic of the disease [29] (rare).
- Generalized pruritus, often accompanied by marked excoriation.
- Pain in involved lymph nodes immediately after the ingestion of alcohol is a curious complaint that is nearly specific to Hodgkin lymphoma; it occurs in fewer than 10% of patients and has no prognostic significance [33].
- Detection of an unusual mass or swelling in the superficial, supradiaphragmatic lymph nodes (60–70% cervical and supraclavicular, 15–20% axillary) is the

most common presentation of Hodgkin lymphoma. Only 15–20% of patients have supradiaphragmatic disease at presentation [34]. Lymphadenopathy is usually nontender and has a "rubbery" consistency.

There are no diagnostic laboratory features of Hodgkin lymphoma.

Biopsy of unexplained, persistent, or recurrent adenopathy should be reviewed by an experienced hematopathologist. The most likely diagnosis is either Hodgkin lymphoma or a non-Hodgkin lymphoma, but clinically enlarged lymph nodes may be associated also with other disorders: infectious, inflammatory, autoimmune, or neoplastic.

Etiology

- Mononucleosis infection: a threefold increased risk of Hodgkin lymphoma in young adults is conferred by a prior history of serologically confirmed infectious mononucleosis.
- Genetic susceptibility and familial aggregation appear to play a role in the incidence of Hodgkin lymphoma. The increased risk of the disease among identical, but not fraternal, twins provides the strongest evidence for a genetic association [35].

Treatment

Current guidelines for the treatment of HL take into account the different effects on fertility of the various regimens [36, 37].

Several chemotherapeutic regimens for HL that include:

- ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine)

Devoid of alkylating agents, pose little or no documented risk of POF [36, 38]. ABVD protocols associated with involved field irradiation are considered standard treatment for limited disease stages.

- Alkylating agents (MOPP, CHOP, BEACOPP)

Protocols containing alkylating agents, especially procarbazine and cyclophosphamide in cumulative doses, are associated with an increased (up to 70%) risk of POF [39].

Damage to the ovarian reserve may only become apparent years later in women still at reproductive age. These protocols are recommended for advanced stages, refractory disease, and relapse.

- HSCT may be required in some cases, associated with highly gonadotoxic conditioning regimens.
- Additional standard therapies include surgery for Hodgkin lymphoma.

Limited-stage disease (defined as asymptomatic stage I or II supradiaphragmatic disease with no bulky sites) treatment:

Involved-field radiotherapy plus anthracycline-containing chemotherapy compared to extended-field radiotherapy in early stages is favorable [40].

Prognosis

Survival expectations at 10 years for patients diagnosed from 2006 to 2010 exceed 90% for patients to age 44 years, 80% for patients to age 54 years, and 70% for patients to age 64 years [41]. These excellent results have been achieved by refining the use of radiotherapy and chemotherapy and improved outcomes for secondary treatments. However, the late effects of treatment for Hodgkin lymphoma remain a concern.

The treatment of Hodgkin lymphoma is associated with important acute and chronic side effects:

Late treatment effects:

- Sterility
- Second malignancy
- Cardiopulmonary disease

These effects are known to contribute to shortened longevity for cured patients. Excess mortality from second malignancy and cardiac disease increase with time and are currently the leading causes of death for Hodgkin lymphoma patients. Recognition and understanding of these problems help to shape primary treatment choice and facilitate optimal follow-up for survivors [29].

Effect on Fertility

Approximately 90% of males are permanently sterilized by six cycles of MOPP chemotherapy [42]. The risk is related to the cumulative dose of alkylating agents such that two to three cycles of MOPP result in azoospermia in approximately 50% of patients [29].

Female fertility after alkylating agent-based treatment is related to age at treatment as well as cumulative alkylating agent dose [43].

The ABVD combination is associated with temporary amenorrhea and azoospermia with full recovery noted in 50–90% of patients [44].

Fertility Preservation Options

As refractory disease and relapse cannot be predicted, fertility issues and preservation methods should be discussed with all patients under the age of 37.

If chemotherapy can be postponed, *embryo or oocyte cryopreservation* should be considered [5]. Unlike in male HL, there is no evidence of pretreatment fertility impairment [45].

Cryopreservation and reimplantation of ovarian cortex have proved effective in women with HL. Several studies have suggested that ovarian tissue transplantation may be considered safe in case of HL [38, 46], but one case report [47]showed ovarian involvement in stage III HL. In some HL cases, large mediastinal masses may increase anesthetic risks, and ovarian tissue harvesting may therefore be contraindicated [5].

Non-Hodgkin Lymphoma

Incidence

The risk of NHL increases with age. NHL incidence rate of increase has slowed in the past two decades, and mortality has declined since 1997. Incidence and mortality for NHL are higher for whites than for African Americans or other racial/ethnic groups in the United States [28].

Non-Hodgkin lymphoma (NHL) is less common than HL in women under 30 years of age [5].

Associated with 5-year survival rates of 69% overall and 84% in women under 20 years of age [5].

Different forms of NHL exist.

Treatment

There are different treatment modalities:

- Local radiation
- Chemotherapy
- Immunotherapy
- HSCT

Most treatment regimens include alkylating agents [5].
Additional standard therapies for NHL are:

- Targeted therapy
- Plasmapheresis
- Watchful waiting
- Biological therapy

Effect on Fertility

There are far fewer data available on fertility after treatment for NHL than HL, though female survivors of childhood NHL appear to be at low risk of POF [48]. Limited studies in adults also report low percentages of gonadal dysfunction [5].

Fertility Preservation Options

Primary care physicians and oncologists should be aware of the available fertility preservation options to expedite referrals to fertility specialists.

Planned treatment protocols and a safe delay before the start of therapy should be discussed with hematologists before considering fertility preservation options. Fertility counselling should be given to all women with reproductive potential and children and their parents, subjected to potentially gonadotoxic treatment. All available methods should be discussed during consultation. In addition, social, legal, and ethical issues should be taken into account [5].

It is difficult to precisely assess the risk of infertility after oncological treatment in children and young women with hematological malignancies, because disease evolution is never completely predictable. Patients initially at low risk of gonadal failure may eventually require more aggressive treatments [49].

The two most important issues are ensuring that the intervention does not harm the patient by dangerously postponing cancer treatment and that no remnant cancer cells are reintroduced by subsequent transplantation, especially in hematological malignancies.

All available methods must be applied to exclude the presence of lymphoma from ovarian biopsies before considering ovarian transplantation [5].

IVM followed by cryopreservation of oocytes or embryos can be an alternative method in adults. Finally, it is imperative to provide the patient clear information on the expected results and risks of the procedures [5].

Sexuality needs to be considered in the care of patients with hematologic malignancies also when patients are older and fertility issues are of less importance. Patients who are treated with chemoimmunotherapy, which entails severe adverse effects, need special attention as this impacts on QoL and probably also sexuality [50].

References

1. Naessen S, Bergstrom I, Ljungman P, Landgren BM. Long-term follow-up of bone density, general and reproductive health in female survivors after treatment for haematological malignancies. Eur J Haematol. 2014;93(2):137–42.
2. Institute NC. A snapshot of leukemia: National Institute of Health. 2014 [cited 2014 November 5]. https://www.cancer.gov/research/progress/snapshots/leukemia.
3. Liesveld JL, Lichtman MA. Acute myelogenous leukemia. In: Lichtman MA, editor. Williams hematology. 8th ed. New York: McGraw-Hill; 2010.
4. Kim MK, Lee DR, Han JE, Kim YS, Lee WS, Won HJ, et al. Live birth with vitrified-warmed oocytes of a chronic myeloid leukemia patient nine years after allogenic bone marrow transplantation. J Assist Reprod Genet. 2011;28(12):1167–70.
5. Jadoul P, Kim SS, Committee IP. Fertility considerations in young women with hematological malignancies. J Assist Reprod Genet. 2012;29(6):479–87.
6. Liesveld JL, and Marshall A. Lichtman.. . Chronic Myelogenous Leukemia and Related Disorders. In: Marshall A. Lichtman ea, editor. Williams Hematology. 1. 8 ed. New York, NY: McGraw-Hill; 2010.
7. Salooja N, Szydlo RM, Socie G, Rio B, Chatterjee R, Ljungman P, et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. Lancet (London, England). 2001;358(9278):271–6.

8. Saunders EF, Lampkin BC, Mauer AM. Variation of proliferative activity in leukemic cell populations of patients with acute leukemia. J Clin Invest. 1967;46(8):1356–63.
9. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med. 2004;350(15):1535–48.
10. Pui C-H. Acute lymphoblastic leukemia. In: Lichtman MA, editor. Williams hematology. New York: McGraw-Hill; 2010.
11. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet (London, England). 2008;371(9617):1030–43.
12. Garcia-Manero G, Yang H, Kuang SQ, O'Brien S, Thomas D, Kantarjian H. Epigenetics of acute lymphocytic leukemia. Semin Hematol. 2009;46(1):24–32.
13. Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, Cortes J, Garcia-Manero G, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006;106(7):1569–80.
14. Oriol A, Ribera JM, Bergua J, Gimenez Mesa E, Grande C, Esteve J, et al. High-dose chemotherapy and immunotherapy in adult Burkitt lymphoma: comparison of results in human immunodeficiency virus-infected and noninfected patients. Cancer. 2008;113(1):117–25.
15. Rasic S, Hadzovic-Dzuvo A, Tomic M, Uncanin S, Coric S. Impact of hemoglobin concentration on plasma B-type natriuretic peptide level and left ventricle echocardiographics characteristics in chronic kidney disease patients. Coll Antropol. 2009;33(Suppl 2):141–4.
16. Rowe JM. Optimal management of adults with ALL. Br J Haematol. 2009;144(4):468–83.
17. Watson M, Wheatley K, Harrison GA, Zittoun R, Gray RG, Goldstone AH, et al. Severe adverse impact on sexual functioning and fertility of bone marrow transplantation, either allogeneic or autologous, compared with consolidation chemotherapy alone: analysis of the MRC AML 10 trial. Cancer. 1999;86(7):1231–9.
18. Brydoy M, Fossa SD, Dahl O, Bjoro T. Gonadal dysfunction and fertility problems in cancer survivors. Acta Oncol (Stockholm, Sweden). 2007;46(4):480–9.
19. Dolmans MM, Marinescu C, Saussoy P, Van Langendonckt A, Amorim C, Donnez J. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. Blood. 2010;116(16):2908–14.
20. Meirow D, Hardan I, Dor J, Fridman E, Elizur S, Ra'anani H, et al. Searching for evidence of disease and malignant cell contamination in ovarian tissue stored from hematologic cancer patients. Hum Reprod. 2008;23(5):1007–13.
21. Familiari G, Caggiati A, Nottola SA, Ermini M, Di Benedetto MR, Motta PM. Ultrastructure of human ovarian primordial follicles after combination chemotherapy for Hodgkin's disease. Hum Reprod. 1993;8(12):2080–7.
22. Dolmans MM, Demylle D, Martinez-Madrid B, Donnez J. Efficacy of in vitro fertilization after chemotherapy. Fertil Steril. 2005;83(4):897–901.
23. Kipps TJC. Chronic lymphocytic leukemia and related diseases. In: Lichtman MA, editor. Williams hematology. 8th ed. New York: McGraw-Hill; 2010.
24. Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL. The clinical and epidemiological burden of chronic lymphocytic leukaemia. Eur J Cancer Care. 2004;13(3):279–87.
25. Kol S, Solt I. GnRH agonist for triggering final oocyte maturation in patients at risk of ovarian hyperstimulation syndrome: still a controversy? J Assist Reprod Genet. 2008;25(2–3):63–6.
26. Coad JE, Matutes E, Catovsky D. Splenectomy in lymphoproliferative disorders: a report on 70 cases and review of the literature. Leuk Lymphoma. 1993;10(4–5):245–64.
27. Ruchlemer R, Wotherspoon AC, Thompson JN, Swansbury JG, Matutes E, Catovsky D. Splenectomy in mantle cell lymphoma with leukaemia: a comparison with chronic lymphocytic leukaemia. Br J Haematol. 2002;118(4):952–8.
28. Instiute NC. A snapshot of lymphoma: National Institute of Health. 2014 [cited 2014]. https://www.cancer.gov/research/progress/snapshots/lymphoma.
29. Horning SJ. Hodgkin lymphoma. In: Lichtman MA, editor. Williams hematology. 8th ed. New York: McGraw-Hill; 2010.
30. MacMahon B. Epidemiology of Hodgkin's disease. Cancer Res. 1966;26(6):1189–201.

31. Clarke CA, Glaser SL, Keegan TH, Stroup A. Neighborhood socioeconomic status and Hodgkin's lymphoma incidence in California. Cancer Epidemiol Biomarkers Prevention (A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology). 2005;14(6):1441–7.
32. Wallace A, Downs E, Gates P, Thomas A, Yates P, Chan RJ. Provision of survivorship care for patients with haematological malignancy at completion of treatment: A cancer nursing practice survey study. Eur J Oncol Nurs (The Official Journal of European Oncology Nursing Society). 2015;19(5):516–22.
33. Atkinson K, Austin DE, McElwain TJ, Peckham MJ. Alcohol pain in Hodgkin's disease. Cancer. 1976;37(2):895–9.
34. Rueffer U, Sieber M, Josting A, Breuer K, Grotenhermen FJ, Bredenfeld H, et al. Prognostic factors for subdiaphragmatic involvement in clinical stage I-II supradiaphragmatic Hodgkin's disease: a retrospective analysis of the GHSG. Ann Oncol (Official journal of the European Society for Medical Oncology). 1999;10(11):1343–8.
35. Mack TM, Cozen W, Shibata DK, Weiss LM, Nathwani BN, Hernandez AM, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. N Engl J Med. 1995;332(7):413–8.
36. Brusamolino E, Bacigalupo A, Barosi G, Biti G, Gobbi PG, Levis A, et al. Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up. Haematologica. 2009;94(4):550–65.
37. Engert A, Eichenauer DA, Dreyling M. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (Official Journal of the European Society for Medical Oncology). 2010;21(Suppl 5):v168–71.
38. Kim SS, Radford J, Harris M, Varley J, Rutherford AJ, Lieberman B, et al. Ovarian tissue harvested from lymphoma patients to preserve fertility may be safe for autotransplantation. Hum Reprod. 2001;16(10):2056–60.
39. Behringer K, Wildt L, Mueller H, Mattle V, Ganitis P, van den Hoonaard B, et al. No protection of the ovarian follicle pool with the use of GnRH-analogues or oral contraceptives in young women treated with escalated BEACOPP for advanced-stage Hodgkin lymphoma. Final results of a phase II trial from the German Hodgkin Study Group. Ann Oncol (Official Journal of the European Society for Medical Oncology). 2010;21(10):2052–60.
40. Ferme C, Eghbali H, Meerwaldt JH, Rieux C, Bosq J, Berger F, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med. 2007;357(19):1916–27.
41. Brenner H, Gondos A, Pulte D. Survival expectations of patients diagnosed with Hodgkin's lymphoma in 2006-2010. Oncologist. 2009;14(8):806–13.
42. Chapman RM, Sutcliffe SB, Rees LH, Edwards CR, Malpas JS. Cyclical combination chemotherapy and gonadal function. Retrospective study in males. Lancet (London, England). 1979;1(8111):285–9.
43. Chapman RM, Sutcliffe SB, Malpas JS. Cytotoxic-induced ovarian failure in women with Hodgkin's disease. I Hormone function I Hormone function e. JAMA. 1979;242(17):1877–81.
44. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. Eur J Cancer Clin Oncol. 1985;21(5):601–5.
45. Leader A, Lishner M, Michaeli J, Revel A. Fertility considerations and preservation in haemato-oncology patients undergoing treatment. Br J Haematol. 2011;153(3):291–308.
46. Seshadri T, Gook D, Lade S, Spencer A, Grigg A, Tiedemann K, et al. Lack of evidence of disease contamination in ovarian tissue harvested for cryopreservation from patients with Hodgkin lymphoma and analysis of factors predictive of oocyte yield. Br J Cancer. 2006;94(7):1007–10.

47. Bittinger SE, Nazaretian SP, Gook DA, Parmar C, Harrup RA, Stern CJ. Detection of Hodgkin lymphoma within ovarian tissue. Fertil Steril. 2011;95(2):803.e3–6.
48. von der Weid NX. Adult life after surviving lymphoma in childhood. Support Care Cancer (Official Journal of the Multinational Association of Supportive Care in Cancer). 2008;16(4):339–45.
49. Jadoul P, Dolmans MM, Donnez J. Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed? Hum Reprod Update. 2010;16(6):617–30.
50. Olsson C, Sandin-Bojo AK, Bjuresater K, Larsson M. Patients treated for hematologic malignancies: affected sexuality and health-related quality of life. Cancer Nurs. 2015;38(2):99–110.

Chapter 5
Nonmalignant Hematologic Diseases

Hemoglobinopathies

Definition

Hemoglobinopathies are a large heterogeneous group of inherited disorders of hemoglobin synthesis affecting the function or levels of hemoglobin. These are the most common inherited red cell disorders worldwide [1].

Hemoglobin is a protein found in red blood cells (RBCs) that is critical for the process of oxygen transportation, allowing oxygen to be transported from the lungs to the tissues. This protein contains two subunits from the α-globin subfamily. Mutated globin proteins or decreased expression of globin proteins (hemoglobinopathies) can lead to poor oxygen transportation and a variety of other damaging physiological outcomes [1].

Hemoglobinopathies can be subdivided into thalassemia syndromes and structural hemoglobin variants [1].

1. The first major subdivision of the hemoglobinopathies, the *thalassemias*, consists of inherited defects in the rate of synthesis (decreased and altered synthesis or agenesis) of one or more of the globin chains. The result is imbalanced globin-chain production, ineffective erythropoiesis, hemolysis, and a variable degree of anemia.
2. The second subdivision consists of conditions, such as *sickle cell* anemia (SCA) that result from mutations within a globin gene, leading to disruption of the normal peptide structure and function; it is an inherited structural alteration in one of the globin chains. Abnormal hemoglobins may be synthesized less efficiently or broken down more rapidly than normal adult hemoglobin; clinical abnormalities result from the physical properties of the abnormal hemoglobin [1].

Sickle cell syndromes and thalassemias constitute a major public health problem.

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_5

Hemoglobinopathies are associated with disease and/or treatment-related morbidity, especially with advancing age. In patients with severe disease or progressive complications, premature mortality in early or mid-adulthood often results [2, 3]. Collectively, these complications result in a deteriorating quality of life (QOL) and function in affected individuals with both disorders [4–7].

The World Health Organization estimated in 2006 that 5% of the world population carries a gene for a hemoglobinopathy, mainly SCA and α- or β-thalassemias [1, 8]. Hemoglobinopathies can be found throughout the world, but prevalence is increased among certain ethnicities [1].

Because the structural hemoglobin variants and the thalassemias occur at a high frequency in some populations not infrequently, multiple hemoglobinopathies will occur concurrently (e.g., βS and β-thalassemia are often seen together in the same individual). Concurrent hemoglobinopathies generally lead to a less severe phenotype.

Thalassemia

Definition

Thalassemia can be defined as a condition in which there is a reduced rate of synthesis of one or more of the globin chains. There are two main classes of thalassemias, α and β, in which the α- and β-globin genes are involved and rarer forms caused by abnormalities of other globin genes [1, 8]. This causes defective adult hemoglobin production and damage to the red cells or their precursors. Thalassemia is not a single disease but a group of disorders, each resulting from an inherited abnormality of globin production [8]. These series of disorders are known collectively as the *thalassemia syndromes* [8]. Thalassemic disorders are the most prevalent monogenic hereditary diseases around the world [9].

α-Thalassemia

α-Thalassemia typically results from functional deletion of two or more of the four α-globin genes. Loss of α-globin chains leads to a reduction in the predominant hemoglobin, hemoglobin A (HbA). Patients with loss of a single α-globin gene are typically asymptomatic silent carriers [8]. Clinical phenotype of α-thalassemia can range from mild effects on hemoglobin indices to fetal hydrops and intrauterine demise, depending on the number of α-globin genes affected and the specific mutations involved.

β-Thalassemia

More than 200 different mutations have been found in association with the β-thalassemia phenotype [8]. The severe homozygous state of an autosomal gene condition is known as *thalassemia major (*most clinically severe form of

β-thalassemia). The heterozygous state is associated with much milder hematologic and clinical changes, thalassemia trait, designated according to their severity as *thalassemia minor or minima* [10]. Later, the term *thalassemia intermedia* was used to describe disorders that were milder than the major form but more severe than the traits, characterized by a later onset and either no transfusion requirement or at least fewer transfusions than are required to treat the major form of the illnesses [8, 1].

β-Thalassemia Minor

The heterozygous state for *β*-thalassemia is usually identified during family studies of patients with more severe forms of *β*-thalassemia, population surveys, or, most frequently, by the chance finding of the characteristic hematologic changes during a routine study.

β-Thalassemia Intermedia

The clinical phenotype of patients designated as having thalassemia intermedia is more severe than the usual asymptomatic thalassemia trait but milder than transfusion-dependent thalassemia major [11, 12].

The syndrome encompasses disorders with a wide spectrum of disability. At the severe end, patients present with anemia later than patients with the transfusion-dependent forms of homozygous *β*-thalassemia and are just able to maintain a hemoglobin level of approximately 6 g/dL without transfusion; at the end patients should be treated with regular transfusion. However, their growth and development are retarded. The patients become seriously disabled, with marked skeletal deformities, arthritis, bone pain, progressive splenomegaly, growth retardation, and chronic ulcerations above the ankles. At the other end of the spectrum, patients remain completely asymptomatic until adult life and are transfusion independent, with hemoglobin levels as high as 10–12 g/dL. All varieties of intermediate severity are observed. Overall, the clinical features of the intermediate forms of *β*-thalassemia are similar to the features of *β*-thalassemia major. Clinically significant iron loading as a result of increased absorption is seen even in patients with infrequent transfusions.

β-Thalassemia Major

β-Thalassemia major (BTM) is a genetic disorder. Affected patients are unable to produce adequate amounts of adult hemoglobin (Hb) and therefore suffer increased anemia in infancy, as the switch from fetal to adult Hb occurs [14]. BTM is a chronic condition that requires patients to use various healthcare resources over the course of their lives to maintain a relatively good quality of life, and patients require a lifelong disease management plan 2 [13]. If untreated, BTM results in life-threatening anemia.

Epidemiology

Thalassemias are the most common monogenic disorders in the world [1]. They occur at a high frequency throughout people of Mediterranean, Arab, or Asian origin. They are also seen commonly in countries in which there has been immigration from these high-frequency populations.

β-Thalassemia major is considered as the most prevalent monogenic hereditary disease. Every year, about 100,000 children afflicted with a new type of this disease are born somewhere in the world [9, 14]. It has been estimated that about 1.5% of the global population (80–90 million people) are carriers of BTM [14].

Pathophysiology

Thalassemia reached its high frequency and genetic diversity because of protection against malarial infections (it is related to past or present heterozygote resistance to *P. falciparum* malaria) [8, 15].

Almost all the pathophysiologic features of the thalassemias can be related to a primary imbalance of globin-chain synthesis. This phenomenon makes the thalassemias fundamentally different from all the other genetic and acquired disorders of hemoglobin production and explains their extreme severity in the homozygous and compound heterozygous states [8]. The pathophysiology of the thalassemias can be traced to the deleterious effects of the globin-chain subunits that are produced in excess.

In *β*-thalassemia, the low β-globin content allows the excess α-globin chains to precipitate and cause cell membrane damage to the red cell precursors and red cells and lead to profound anemia; the resultant ineffective erythropoiesis found in patients, if severe, may necessitate frequent blood transfusion. This causes expansion of the ineffective marrow, with severe effects on development, bone formation, and growth. The major cause of morbidity and mortality is the effect of iron deposition in the endocrine organs, liver, and heart, which results from increased intestinal absorption and the effects of blood transfusion [1, 8]. The pathophysiologic mechanisms provide the basis for the remarkably diverse clinical findings in the thalassemia syndromes [16].

Clinical Manifestations

The clinical pictures of *α*- and *β*-thalassemia vary widely, and genetic and environmental factors modify different phenotypes [8]. Globin-chain imbalance is the major factor determining the severity of the thalassemias. All the manifestations of *β*-thalassemia can be related to excess *α*-chain production. Thus, any mechanism that reduces the excess of *α*-chains should reduce the clinical severity of the disease.

β-globinopathy-affected infants are well at birth, and clinical manifestations typically appear 6–12 months after birth when γ-globin expression, which is the predominate globin expressed from the β-globin family during fetal life, begins to diminish to residual amounts. Disease severity may range from asymptomatic to severe. A later onset suggests the condition will develop into one of the intermediate forms of *β*-thalassemia [8].

The profound anemia of homozygous *β*-thalassemia causes severe tissue hypoxia, and anemia usually becomes progressively more severe. The infants fail to thrive and may have feeding problems, bouts of fever, diarrhea, and other gastrointestinal symptoms. Few of the complications of the disorder occur during childhood.

The course of the disease in childhood depends almost entirely on whether the child is maintained on an adequate transfusion program [8, 16]. The disease presents a problem only when the effects of iron loading resulting from ineffective erythropoiesis and from repeated blood transfusions become apparent at the end of the first decade. Children who have grown and developed normally throughout the first 10 years of life as a result of regular blood transfusion begin to develop the symptoms of iron loading as they enter puberty, particularly if they have not received adequate iron chelation [8, 16]. Children who are treated with an adequate iron chelation regimen develop normally, although some of them remain short in height [8].

An inadequately transfused child develops the typical features of *Cooley anemia* characterized by severe anemia with frequent complications:

- Growth is stunted.
- Overgrowth of the maxillary region, the face gradually assumes a "mongoloid" appearance. Maxillary deformities often lead to dental problems from malocclusion.
- Radiologic appearance of the skull, long bones, and hands and gross skeletal deformities can occur: spontaneous fractures occur commonly as a result of the expansion of the marrow cavities with thinning of the long bones and skull.
- Liver and spleen are enlarged.

Gross splenomegaly may occur and secondary thrombocytopenia and leukopenia frequently develop, leading to a further tendency to infection and bleeding. Splenectomy is frequently performed to reduce transfusion frequency and severe thrombocytopenia; however, postsplenectomy infections are particularly common [8]:

- Pigmentation of the skin increases.
- Features of a hypermetabolic state, as evidenced by fever, wasting, and hyperuricemia, may develop [8].
- Infection is a common cause of death. All forms of severe thalassemia appear to be associated with an increased susceptibility to bacterial infection. The reason is not known. The relatively high serum iron levels may favor bacterial growth. Another possible mechanism is blockade of the monocyte–macrophage system as a result of the increased rate of destruction of red cells. Transfusion-dependent patients with thalassemia are at particular risk for blood-borne infections

including hepatitis B, hepatitis C, HIV/AIDS, and, in some parts of the world, malaria. Blood-borne infection, notably with hepatitis B or C [17], HIV, or malaria [18], is extremely common in some populations, although the frequency is decreasing with the use of widespread blood-donor screening programs.
- Formation of massive deposits of extramedullary hematopoietic tissue may cause neurologic complications.
- Coagulation defects.

Patients, particularly after splenectomy and with high platelet counts, may develop progressive pulmonary arterial disease as a result of platelet aggregation in the pulmonary circulation. There is increasing evidence that the hemolytic component of the anemia of β-thalassemia is associated with the release of hemoglobin and arginase resulting in impaired nitric oxide availability and endothelial dysfunction with progressive pulmonary hypertension [19]. Bleeding tendency may be seen in the absence of thrombocytopenia. Epistaxis is particularly common. These hemostatic problems are associated with poor liver function in some cases [8]:

- Chronic leg ulceration may occur but is more common in thalassemia intermedia.

Abnormal Iron Metabolism

β-Thalassemia homozygotes that are anemic manifest increased intestinal iron absorption that is related to the degree of expansion of the red cell precursor population. Iron absorption is decreased by blood transfusion [8, 16].

Most patients homozygous for β-thalassemia require regular blood transfusion; thus, transfusional siderosis adds to the iron accumulation. Iron accumulates in the skin leading to increased pigmentation, in the liver, and, most importantly, in the myocardium [8, 20]:

- Cardiac siderosis.
- Iron accumulation in the myocardium leads to death by involving the conducting tissues or by causing intractable cardiac failure [8] . Toward the end of the second decade, cardiac complications arise, and death usually occurs in the second or third decade as a result of cardiac siderosis [20–22]. Cardiac siderosis may cause an acute cardiac death with arrhythmia or intractable cardiac failure. Both of these complications can be precipitated by intercurrent infection [8, 23].
- Endocrine disturbances caused by iron loading.

Iron accumulates in the endocrine glands, particularly in the parathyroids, pituitary, and pancreas. Other consequences of iron loading are:

- Diabetes mellitus (over the succeeding years).
- Abnormalities of hypothalamic–pituitary function leading to growth retardation. Absence of the pubertal growth spurt and failure of the menarche. Delayed puberty, hypogonadism, and growth retardation are common and probably reflect hypogonadotrophic hypogonadism and damage to the pituitary gland [17, 24].

Osteoporosis is being recognized increasingly and may, at least in part, be a reflection of hypogonadism [8, 17].
- Growth hormone deficiency.
- Hypothyroidism and adrenal insufficiency (hypoparathyroidism) also occur but are less common [23].

Laboratory Features

The anemia of β-thalassemia has three major components:

- Ineffective erythropoiesis with intramedullary destruction of a variable proportion of the developing red cell precursors
- Hemolysis resulting from destruction of mature red cells containing α-chain inclusions
- Hypochromic and microcytic red cells that result from the overall reduction in hemoglobin synthesis [8]

Laboratory Features in β-Thalassemia Major

Hemoglobin levels at presentation may range from 2–3 g/dL or even lower. The red cells show marked anisopoikilocytosis, with hypochromia. The appearance of the blood film varies, depending on whether the spleen is intact [8].

Carrier states for the thalassemias can be identified, and affected fetuses can be diagnosed by DNA analysis after the ninth to tenth week of gestation [8]. The examination of siblings, parents, and children can be very important in confirming the diagnosis by finding the abnormalities in other family members, and the examining physician should make every effort to obtain a complete blood count in family members.

Differential Diagnosis

The clinical and hematologic findings in homozygous β-thalassemia are so characteristic that the diagnosis usually is not difficult.

Treatment

General Care

Management of thalassemia requires a high standard of general pediatric care.

Symptomatic management is based on:

- Lifelong regular red cell transfusions
- Iron chelation therapy in an attempt to prevent iron overload
- Judicious use of splenectomy in cases complicated by hypersplenism
- Good standard of general pediatric care [4]

Particular attention should be paid to the ear, nose, and throat because of chronic sinus infection and middle ear diseases resulting from bone deformity of the skull. In case of infection, it has to be treated early. Regular dental surveillance is essential because poorly transfused thalassemic children have a variety of deformities of the maxilla and poorly developed teeth.

In the later stages of the illness, when iron loading becomes the major feature, endocrine replacement therapy may be necessary. Symptomatic treatment for metabolic bone disease and cardiac failure also may be needed [8].

Transfusion

Children with β-thalassemia who are maintained at a hemoglobin level of 9.5–14.0 g/dL grow and develop normally. They do not develop the distressing skeletal complications of thalassemia. A transfusion program should not be started too early, and it should be initiated only when the hemoglobin level is too low to be compatible with normal development. If transfusion is started too soon, thalassemia intermedia may be missed, and the child may be transfused unnecessarily. Usually blood transfusions are given every 4 weeks on an outpatient basis. To avoid transfusion reactions, washed, filtered, or frozen red cells should be used so that the majority of the white cells and plasma-protein components are removed [8].

Effect on Fertility of Iron Overload

Nowadays, the major problems dealing with adult BTM patients are fertility and osteoporosis [25–27].

Patients with BTM suffer from severe anemia and are dependent on blood transfusion, which in turn is responsible for tissue hemosiderosis. Massive tissue iron deposition affects all organ systems, especially the cardiac, hepatic, and endocrine systems.

Adequate blood transfusion and intensive iron chelation therapy have markedly improved the prognosis of these patients. Despite frequent blood transfusion and iron chelation, the risk of secondary endocrine dysfunction remains high.

Hypogonadism is one of the most frequent endocrine complications, mostly due to gonadotropin deficiency secondary to siderosis of the pituitary gland [28, 29].

Endocrine complications due to hemosiderosis are present in a significant number of patients with BTM worldwide and often become barriers in their desire for parenthood. Iron toxicity has been implicated as a major contributor to reduced

fertility and adverse pregnancy outcomes in thalassemia. Although spontaneous fertility can occur, the majority of females with BTM are infertile and need assisted reproductive techniques. Current improvements in the management of thalassemia disorders offer patients the possibility of having a regularly functioning reproductive system and increased chances of achieving a pregnancy [14]. Also, pregnancies have occurred among women with documented hypogonadism, many receiving hormone replacement therapy [30, 31]. This may relate to the lack of precision of common laboratory testing in defining ovarian reserve or fertility potential. The more recent use of MRI technology combined with ultrasound methods to assess ovarian volume and antral follicle counts and measurement of levels of inhibin B and anti-Mullerian hormone may provide more accurate predictions of ovarian reserve [32, 33].

Female

The commonest abnormality is hypogonadotropic hypogonadism (HH) associated with primary amenorrhea, anovulation, delayed puberty, or secondary amenorrhea with consequent infertility, attributed to the iron effect on the pituitary gland as well as on the female reproductive system. Early recognition and prevention of the endocrine complications, by early and regular chelation therapy, are mandatory for the improvement of the quality of life of these patients [34]. In BTM, iron overload is the consequence of multiple blood transfusions and an inappropriately increased iron absorption associated with ineffective erythropoiesis [35]. There is an excess on the iron-carrying capacity of transferrin that results in the emergence of nontransferrin-bound iron (NTBI), which catalyzes the formation of free radicals, resulting in oxidative stress (OS) and damage to mitochondria, lysosomes, lipid membranes, proteins, and DNA [35]. Thus, thalassemics are in a state of enhanced OS [36]. Infertility in these women seems to be attributed to iron deposition and iron-induced oxidative stress (OS) in various endocrine organs, such as the hypothalamus, pituitary, and female reproductive system, and also through the iron effect on other organs, such as the liver and pancreas, contributing to the impaired metabolism of hormones and serum antioxidants.

Using appropriate combination of antioxidants and iron chelators, essential trace elements and minerals could probably reduce the extent of oxidative damage, neutralize the deleterious effects of reactive oxygen species (ROS) [37], and probably reverse endocrine complications, improving reproductive ability, related complications, and fertility potential [38].

Meanwhile, recent advances in the management of BTM have significantly improved life expectancy and quality of life of BTM patients, with a consequent increase in their reproductive potential and desire to have children [30].

However, endocrine complications due to hemosiderosis are still present in a significant number of patients worldwide and often become a barrier in their desire for parenthood [36].

Male

Failure of pubertal growth, delay or absence of sexual development, infertility, and sexual dysfunction due to hypogonadism and defective spermatogenesis are well-recognized disturbances among male patients with BTM. These problems are attributed mainly to the damage caused by chronic anemia and deposition of hemosiderin in the pituitary gland and testicles. Ineffective erythropoiesis results in increased absorption of iron. Adequate blood transfusion and iron chelation to keep serum ferritin concentrations <2.500 ng/mL have markedly improved survival and decreased complications of thalassemic patients. This longevity has changed the pattern of morbidity of adult patients with thalassemia [25].

The improved long-term survival of BTM patients has resulted in increased focus on the ability to preserve fertility.

Iron Chelation

Every child who is maintained on a high transfusion regimen ultimately develops iron overload and dies of siderosis of the myocardium. Therefore, such children must be started on a program of iron chelation within the first 2–3 years of life. Deferoxamine (desferrioxamine) was the first chelating agent of proven long-term value for treatment of thalassemia [36]. Chelation therapy should commence by the time the serum ferritin level reaches approximately 1000 mcg/dL. In practice, this level usually is seen after the 12th–15th transfusion. To prevent toxicity, infants must not be overchelated when the iron burden is still low.

Stem Cell Transplantation

Go to page where AHSC is described with effect on fertility.

Gene Therapy

Numerous therapies are currently in clinical trials or in development, including therapies utilizing gene replacement therapy using lentiviruses and the latest gene editing techniques. In addition, methods are being developed that may be able to expand gene therapies to those with poor access to medical care [1]. Experimental approaches to their management include the stimulation of fetal hemoglobin synthesis and attempts at somatic cell gene therapy [8]. Hemoglobinopathies, especially SCA, are prime targets for gene therapy for a variety of reasons. Their high prevalence, significant morbidity and mortality, and the resulting high cost of medical care portends that a curative therapy can greatly improve patient outcomes and significantly reduce associated medical costs. With regard to gene editing strategies, many of the mutations resulting in hemoglobinopathies are single-point

mutations, which typically allow for greater gene-correction efficiencies than more complex mutations. Gene therapy utilizing a patient's autologous stem cells holds great promise (this therapy utilizes patient's own cells), as they would obviate the need to identify matched donors and further mitigate the morbidity and mortality of allogenic HSCT. Given the successes of these therapies both in clinical trials and in development, gene therapy has the potential to have a profound impact providing a curative therapy to all patients on the treatment of hemoglobinopathies [1]. Cord blood and HLA haploidentical transplantation have been used in a small number of patients with SCD, but graft failure remains a significant issue [39–41].

Prognosis

The prognosis for patients with severe forms of β-thalassemia who are adequately treated by transfusion and chelation has improved dramatically over the years. Adequate transfusion and chelation are associated with longevity and good quality of life. On the other hand, poor compliance or unavailability of chelating agents is still associated with a poor prospect of survival.

Prevention

Prenatal diagnosis for prevention of thalassemia entails screening mothers at the first prenatal visit, screening the father in cases in which the mother is a thalassemia carrier, and offering the couple the possibility of prenatal diagnosis and termination of pregnancy if both mother and father are carriers of a gene for a severe form of thalassemia. These programs are devoted mainly to prenatal diagnosis of the severe transfusion-dependent forms of homozygous β^{+}- or β^{0}-thalassemia. Several approaches continue to be explored in an attempt to avoid the use of invasive procedures like chorion villous sampling. A variety of methods are being used to harvest fetal DNA from fetal cells in maternal blood or from maternal plasma [42, 43], and there are increasing numbers of attempts at preimplantation diagnosis of thalassemias [44].

Sickle Cell Disease

Definition

A glutamic acid to valine substitution at the sixth amino acid of the β-globin chain of human hemoglobin (HbA) results in formation of sickle hemoglobin (HbS) composed of two α-globin peptides and two mutated β-globin peptides (α2βS2),

instead of the normal HbA (α2β2). Sickle cell disease (SCD) results from homozygosity for this mutation or from a compound heterozygosity for sickle hemoglobin and *β*-thalassemia or another *β*-globin variant [45]. It is the most common structural hemoglobinopathy.

It is a multisystem disorder characterized by anemia, increased hemolysis and vaso-occlusive episodes [46]. Sickle cell anemia (HbSS, SCA) is a chronic, hemolytic anemia that results in progressive organ damage and a shortened life span [1–3] [47].

Besides SCA, several other structural hemoglobin variants exist (e.g., hemoglobin C, D, and E). All of the structural hemoglobin variants are inherited in an autosomal recessive manner, and compound heterozygotes for any of these variants along with a sickle allele (HbSC, HbSD, or HbSE) phenotypically result in SCD.

Inheritance of only one HbS allele is termed *sickle cell trait* (HbAS). Individuals have one copy of βS. An estimated 300 million people carry the trait worldwide [48]. The percentage of HbA is always higher (~60 %) than HbS (~40 %) in sickle cell trait. HbAS is considered a generally asymptomatic state.

Epidemiology

The global disease burden of hemoglobinopathies is borne enormously by the African continent. Sickle cell anemia is highly prevalent among people with sub-Saharan African or Indian ancestry [1]. According to the WHO, 5–16% of under-five mortality in some areas of sub-Saharan Africa is attributed to SCA http://apps.who.int/gb/archive/pdf_files/WHA59/A59_9-en.pdf. Additionally, data suggest that children born in Africa with SCA have an early-life mortality of 50–90% [49]. In the United States, the Centers for Disease Control and Prevention estimates that sickle cell anemia is present in 1 in 500 live births among Americans of African descent; 1 in 12 American of African descent has the trait, and approximately 100,000 Americans largely of African descent live with the disease. In Americans of Hispanic descent, the rate of SCD is 1 in 36,000 live births. Accurate population statistics of SCD are difficult to obtain in the United States because of a lack of standardized data collection and central reporting [46]. There are approximately 300,000 affected infants born yearly worldwide [49].

Pathophysiology

HbS is prone to polymerization (hemoglobin polymerization) under reduced oxygen conditions. Membrane changes leading to potassium loss and cellular dehydration; interaction of sickle hemoglobin with microvascular endothelium, neutrophils, and monocytes; hemolysis; nitric oxide depletion; aggregation of RBC and

adhesion of white blood cells (WBCs) in the microvasculature (abnormal cell adhesiveness); release of inflammatory proteins; and activation of coagulation are the processes which lead to a hemolytic anemia, an inflammatory state, ischemia–reperfusion injury, painful vaso-occlusive episodes, and damage to multiple organ systems with a resultant shortened life expectancy. This process can lead to a variety of significant adverse sequelae of varying severity.

There is considerable heterogeneity in the severity of the disease; the best known modifier of the disease is an elevated level of fetal hemoglobin (HbF), which exerts a potent anti-sickling effect [45].

Laboratory Features

Sickle cell anemia is characterized by a laboratory profile of evidence of hemolytic anemia and increases in:

- Lactate dehydrogenase (LDH)
- Indirect bilirubin
- Reticulocyte count

Anemia is usually normochromic and normocytic with an Hb level between 5 and 11 g/dL. The red cell density is increased with a normal mean cell Hb concentration (MCHC). Serum erythropoietin level is decreased relative to the degree of anemia [45]. Elevated neutrophil and platelet levels are observed even in asymptomatic patients reflective of persistent low-grade inflammation [45].

Course and Prognosis

Mortality from SCD in the United States has declined since 1968, coinciding with the introduction of pneumococcal polyvalent conjugate 7 (PVC7) vaccine. Average life expectancy of patients with HbSS disease in the United States is 42 and 48 years for males and females, respectively. As the sickle cell population ages, causes of death change from an infectious etiology to those related to end-organ damage, such as renal failure [45].

Clinical Manifestations

The manifestations of SCD are chronic and progressive. Despite advances in management, patients remain at high risk of significant morbidity and early death [46].

Sickle Cell Crises

The typical course for a sickle cell patient is that of periods of relatively normal functioning despite chronic anemia and ongoing vasoocclusion, punctuated by periods of increased pain, and serial changes in various laboratory parameters that are termed "a sickle cell crisis." Crises have typically been classified as VOEs, aplastic crises, sequestration crises, and hyperhemolytic crises.

Vaso-occlusive Crises

It is the most common clinical manifestation. It results from increasing vasoocclusion causing tissue hypoxia, which manifests as pain. Vasoocclusion may affect any tissue, but patients typically have pain in the chest, lower back, and extremities. Abdominal pain may mimic acute abdomen from other causes. Each patient's recurrences usually mimic the same pattern of pain. Fever is often present, even in the absence of infection. Episodes may be precipitated by dehydration, infection, and cold weather although in about most cases, no precipitating factor is found [50].

Aplastic Crises

Aplastic crises in sickle cell anemia result when there is a marked reduction in red cell production in the face of ongoing hemolysis, causing an acute, severe drop in Hb level.

Sequestration Crises

This type of crisis is characterized by sudden, massive pooling of red cells, typically in the spleen and less commonly in the liver [51]. Splenectomy is recommended after the first episode of life-threatening splenic sequestration crisis or chronic hypersplenism. Partial splenectomy and emergency splenectomy during a crisis is not recommended. Parental education is important for early recognition of the problem so they can seek medical care promptly [52].

Hyperhemolytic Crisis

This is characterized by decreased Hb, increasing reticulocytes, hyperbilirubinemia, and increased LDH.

Pain

Patients with SCD have acute pain, chronic pain, or both.

Pulmonary Manifestations

The acute chest syndrome (ACS) is a constellation of signs and symptoms in patients with SCD that includes a new infiltrate on chest radiograph defined by alveolar consolidation, chest pain, fever, tachypnea, wheezing or cough, and hypoxia.

Cardiac Manifestations

Anemia in SCD results in an elevated cardiac output secondary to an increased volume with minimal increase in heart rate [53].

Central Nervous

Stroke in SCD is a macrovascular phenomenon with devastating consequences that affects approximately 11% of patients younger than 20 years of age [54].

Genitourinary Systems

Renal Failure Sickling of HbSS erythrocytes in the hypoxic, acidic, and hypertonic environment of the renal medulla, oxidative stress, increase in prostaglandins and endothelin-1 in the kidney, and abnormalities of the renin angiotensin system contribute to the pathophysiology of renal disease in SCD [55].

Priapism

Priapism is prevalent in at least 35% of male patients with SCD with devastating psychological consequences; true prevalence may be higher [56].

Nocturnal Enuresis

Social and environmental factors, decreased functional bladder capacity, and decreased arousal during sleep appear to be contributing factors.

Musculoskeletal System

Bone marrow hypercellularity is thought to predispose to this phenomenon by causing a decrease in local blood flow and oxygenation causing musculoskeletal pain.

Osteomyelitis, Septic Arthritis, and Bone Infarction

Impaired cellular and humoral immunity together with infarction of the bone contribute to this complication with an estimated prevalence of 12%. Atypical serotypes of *Salmonella*, *S. aureus*, and Gram-negative bacilli are the principal infectious offenders [45].

Osteopenia and Osteoporosis

Osteopenia and osteoporosis are prevalent (30–80%) in patients with sickle cell anemia, with a predilection for the lumbar spine. Etiology of osteoporosis is multifactorial with hypogonadism, hypothyroidism, nutritional deficiencies, and iron overload interfering with osteoblast function being the major causes [45].

Avascular Necrosis

Vasoocclusion resulting in infarction of articular surfaces of the long bone occurs most commonly in the femur followed by the humerus [45].

Ophthalmic Complications: (Sickle Cell Retinopathy)

Splenic Complications:

- Functional asplenia occurs in 86% of infants with SCD [45].
- Leg ulcers.
- Hepatobiliary complications.

Treatment

Increase Fetal Hemoglobin Levels

The observation that HbF results in ameliorating the phenotype of SCD led to research focused on HbF modulation as a therapy for SCD.

Transfusion

Similar to severe thalassemia, patients with severe SCD often require frequent blood transfusions and are at risk of transfusion-induced iron overload. Red cell transfusions are used frequently on an acute or chronic basis.

Indications for Acute Red Cell Transfusion

- Symptomatic anemia
- ACS
- Stroke
- Aplastic and sequestration crises
- Major organ damage secondary to vasoocclusion
- Priapism
- Prior to major surgery or surgery involving critical organs

Indications for Chronic Transfusion

- Stroke
- Abnormal TCD velocity

Hydroxyurea

It is the only FDA-approved agent for the treatment of SCD. It is a ribonucleotide reductase inhibitor and is S-phase specific in the cell cycle.

Pain Control

Acute pain is managed with opioids, nonsteroidal anti-inflammatory drugs, acetaminophen, or a combination of these medications. A multidisciplinary approach is needed for pain management, especially if chronic pain is present. Opioid side effects should be anticipated and managed. Antidepressants, anticonvulsants, and clonidine can be used for neuropathic pain. Occasionally, severe, unrelenting pain may require red cell transfusion to decrease sickle Hb below 30% in the blood [45].

Hematopoietic Stem Cell Transplantation (HSCT)

Gene Therapy

Effect on Fertility

Some of the reproductive issues in SCD arise due to chronic medical therapies that are used increasingly to prevent or manage SCD-related morbidity [57]. It is important to counsel patients about the impact of these treatments on their ovarian function and discuss fertility preservation options prior to BMT.

Infertility in men with SCD has been studied more frequently than infertility in women and appears to have multiple causes, including hypogonadism, sperm abnormalities, and erectile dysfunction (ED) due to priapism. Although a delay in sexual maturation of 1.5–2 years, on average, occurs in adolescents and young adults with SCD [58, 59], most will have normal sexual maturation. Studies are inconsistent as to whether primary testicular failure or secondary hypothalamic–pituitary dysfunction [60, 61] is the cause. Up to 24% of men with SCD may develop hypogonadism, a clinical syndrome associated with poor testosterone production, infertility, ED, and poor libido [60].

Clinical characteristics include sparse facial, pubic, and axillary hair and small testicular size.

Clinical laboratory findings are low testosterone levels with variable follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels [61].

Sperm abnormalities are frequent in males with SCD, with rates as high as 91% [62]. Low sperm density, low sperm counts, poor motility, and increased abnormal morphology occur more frequently in males with SCD than in controls [63].

Currently, there is no consensus on whether women with SCD are at increased risk for infertility or if well-described data on delayed puberty and adverse outcomes are associated with pregnancy [57].

Long-Term Therapies and Reproductive Issues

Long-term therapies such as chronic transfusion, hydroxyurea (HU), and hematopoietic stem cell transplantation (HSCT) have reduced SCD-related morbidity.

As utilization of these therapies increases, associated adverse effects and toxicities need to be evaluated.

Iron Overload

Endocrinopathy from transfusional iron overload is manifested as hypothyroidism, diabetes mellitus, growth failure, and gonadal dysfunction, and all appear to be more common in thalassemia than in SCD [64]. In addition, fertility preservation after HSCT and the endocrine abnormalities associated with transfusional iron overload remain concerns.

HU

Close monitoring for sperm abnormalities during HU therapy with serial sperm analyses every 6–12 months has been suggested [65]. There is a theoretical risk of HU affecting sperm development given that it is an antimetabolite [65]. HU is a ribonucleotide reductase inhibitor primarily acting as an S-phase-specific cytotoxic

agent that impairs DNA synthesis. These effects are relatively short-lived once the drug is removed. Therefore, once-daily administration of HU has brief, intermittent cytotoxic effects on dividing cells [57, 65]. There is strong and increasing evidence that hydroxyurea (HU) is beneficial for many patients with SCA, but does not provide a cure. Issues have been raised regarding HU use, abnormal sperm production, and teratogenic effects. Because women with SCD are at risk for pregnancy-related complications as well as the potential teratogenic effects of HU, contraception counseling is important to avoid unplanned pregnancies. Hormonal contraceptive use is controversial in SCD primarily due to the theoretical increased risk for venous thromboembolism and risk for acute pain events [57]. There is limited data on the effect of HU on ovarian function in patients with SCA; however, gonadotoxicity has been described in males with SCA. Decreased spermatogenesis and sperm motility in adult males on HU for SCA have been described, with reports of both permanent and reversible azoospermia. Potential side effects of gonadal dysfunction should be discussed before the initiation of HU, and regular monitoring of gonadal function should occur while on HU therapy. Potential side effects of gonadal dysfunction should be discussed before the initiation of HU, and regular monitoring of gonadal function should occur while on HU therapy.

BMT

As both treatment with HU and treatment with BMT are [66] associated with gonadal dysfunction, they may exacerbate this risk in those with SCA. It is important to counsel patients about the impact of these treatments on their ovarian function and discuss fertility preservation options when possible prior to BMT.

Awareness of the possibility of diminished ovarian reserve and premature ovarian insufficiency in females with SCA who are to be treated with HU or BMT will allow for opportunities to refer to a reproductive specialist for additional counseling when appropriate [66].

Lukusa et al. assessed the long-term effects of BMT or HU on endpoints of fertility in ten male patients with SCD. These authors found that 50% of the subjects who received a BMT and 50% of subjects who had received HU were azoospermic. Impairment of spermatogenesis was thought to be related to the duration of HU therapy [67, 68].

Fertility Preservation

The increase in the proportion of childhood and adolescent cancer survivors, as well as those who have undergone chemoradiation for nonmalignant conditions, has been the main impetus for the increasing demand for fertility preservation methods in younger age groups. There is growing consensus that individuals at risk for gonadal failure after exposure to gonadotoxic drugs should be offered fertility preservation.

Cryopreservation options have expanded and depend on stage of pubertal development.

Cryopreservation of sperm in pubertal males is standard, and improvement of sperm banking techniques and increased use of intracytoplasmic sperm injection may increase successful outcomes [69].

Cryopreservation of testicular tissue, considered experimental, is an option in prepubertal boys, but is waiting for the development of technology and procedures for restoring human fertility [69].

Preservation of embryos, mature oocytes, and ovarian tissue is an option for females before HSCT [70].

Cryopreservation of mature oocytes has advanced to the point that this procedure is no longer considered experimental [71]. The procedure requires that women undergo treatment with hormonal therapy to stimulate increased production of mature oocytes. It should be noted, however, that women with SCD are at risk for thromboses and increased acute pain while being exposed to increased estrogen levels during ovarian stimulation. Successful oocyte preservation after controlled ovarian stimulation in a 19-year-old woman with SCD has been described using a protocol to avoid hyperstimulation and incorporating anticoagulation for thrombosis prevention [72]. Although oocyte collection was successful, the patient required hospitalization for pain management postoperatively.

In addition, successful pregnancies in women with SCD after ovarian tissue preservation have been reported [73]. For girls who are _18 years of age, particularly those _12 years, ovarian tissue preservation is an option, although outcomes in SCD are not clear [74].

Ovarian tissue cryopreservation and GnRH agonist-induced ovarian suppression during chemotherapy are increasingly widely used in adults.

At present, ovarian tissue cryopreservation is the only option to preserve fertility in prepubertal girls and is one option available to those who are peripubertal. This requires a moderately invasive laparoscopic procedure. However, some patients may prefer this approach as it circumnavigates cultural issues surrounding the topic of sexuality that can arise from the adolescent or her family regarding the transvaginal procedures routinely performed during oocyte cryopreservation.

Exacerbation of hypogonadism in males with SCA treated with HU has been identified. It is important to counsel parents (as surrogate decision-makers), and patients (when at an appropriate and mature age), about the risk of impaired fertility with HU therapy, and before beginning HU the possibility of sperm banking has to be mentioned [66]. Consensus reports on HU use in SCD suggest that sperm banking or cryopreservation of testicular tissue should be offered before starting HU [75].

Myeloablative conditioning regimens before HSCT for SCD cause infertility, particularly in females [57]. The risk of impaired fertility after HSCT depends on many factors, including exposure to pelvic radiation, gonadotoxic chemotherapeutic agents, and stage of pubertal development at the time of transplantation. It is important to counsel patients about the impact of treatments on their ovarian

function and discuss fertility preservation options when possible prior to BMT. Patients may opt for procedures to preserve fertility before HSCT regardless of conditioning regimens.

Patients with SCD have success with procedures and therapies that preserve fertility [73].

Aplastic Anemia

Definition

Aplastic anemia (AA) is an unusual hematologic disorder characterized by bone marrow hypocellularity and peripheral blood pancytopenia [76].

AA is defined as a clinical syndrome characterized by pancytopenia with a hypocellular bone marrow in the absence of abnormal infiltration or increased reticulin [77].

Severe aplastic anemia is a rare hematologic disease that results in immune-mediated bone marrow failure [78].

Aplastic anemia may be acquired or inherited [77].

Acquired aplastic anemia is a clinical syndrome in which there is a deficiency of marrow blood cell production; red cells, neutrophils, monocytes, and platelets in the blood; and fatty replacement of the marrow with a near absence of hematopoietic precursor cells. It is an autoimmune process. Neutropenia, monocytopenia, and thrombocytopenia, when severe, are life-threatening because of the risk of infection and bleeding, complicated by severe anemia.

The disease may be stratified into moderately severe, severe, and very severe acquired aplastic anemia based on the blood counts (especially the neutrophil count) and the degree of marrow hypocellularity.

Most cases of aplastic anemia are acquired; fewer cases are the result of an *inherited disorder*, such as Fanconi anemia, Shwachman–Diamond syndrome, and others.

Epidemiology

Severe aplastic anemia in children and adolescents is a rare disease with an estimated incidence of 1–3 cases per million [79].

Aplastic anemia is a rare disorder most with a bimodal age presentation, arising both early and late in life [79].

Aplastic anemia in the United States is predominantly a disease of Caucasians, and it also occurs in African Americans albeit less frequently [78].

Aplastic anemia (AA) is a diagnosis that can present in any age group [77].

Sever aplastic anemia has an incidence of approximately 2 per million per year [78].

Incidence of Acquired Aplastic Anemia

Approximately 2 per 1,000,000 persons per year. This annual incidence has been confirmed in studies in Spain (Barcelona), Brazil (State of Parana), and Canada (British Columbia). The highest frequency of aplastic anemia occurs in persons between the ages of 15 and 25 years; a second peak occurs between the ages of 65 and 69 [80].

Aplastic anemia is more prevalent in Asia, (Thailand, Malaysia, among children of Asian descent living in Canada).

The explanation for a twofold or greater incidence in the Orient compared to the Occident may be multifactorial, but a predisposition gene or genes are a likely component. The male-to-female incidence ratio of aplastic anemia in most studies is approximately one.

Seronegative viral hepatitis is a forerunner of approximately 7% of cases of acquired aplastic anemia [80].

Etiology and Pathophysiology

Acquired

Acquired forms of AA are believed to be the result of an autoimmune attack directed at hematopoietic progenitor cells. The immune attack is primarily directed by cytotoxic T cells that target hematopoietic stem cells and cause apoptosis leading to hematopoietic failure. It remains unclear which antigens the T cells are targeting [77].

- High-risk drugs:
  - Alkylating agents (busulfan, cyclophosphamide, melphalan)
  - Antimetabolite (fluorouracil, mercaptopurine, methotrexate)
  - Cytotoxic antibiotic (daunorubicin, doxorubicin, mitoxantrone)
  - Idiosyncratic response to certain pharmaceuticals (e.g., ticlopidine, chloramphenicol)
- Prolonged high-dose exposure to certain toxic chemicals: benzene.
- Specific viral infections: Epstein–Barr virus, HIV, non-A, non-B, non-C, and non-D hepatitis.
- Connective tissue or autoimmune diseases: LES.
- Radiotherapy and chemotherapy.
- Rarely in association with pregnancy.
- Most cases occur without an evident precipitating cause and are caused by autoreactive cytotoxic T lymphocytes that suppress or destroy multipotential hematopoietic cells.

Inherited

Inherited forms may result from DNA repair defects (Fanconi anemia, FA), abnormal telomere physiology (dyskeratosis congenita, DKC), or abnormalities of ribosomal biogenesis (Shwachman–Diamond syndrome) [77].

- Fanconi anemia
- Dyskeratosis congenita
- Shwachman–Diamond syndrome
- Other rare syndromes

The final common pathway to the clinical disease is a decrease in blood cell formation in the marrow. The number of marrow CD34+ cells (multipotential hematopoietic progenitors) and their derivative colony-forming unit-granulocyte–macrophage (CFU-GM) and burst-forming unit-erythroid (BFU-E) are reduced markedly in patients with aplastic anemia [80].

Clinical Features

The onset of symptoms of aplastic anemia may be gradual and generally are results of:

- *Anemia*: pallor, weakness, dyspnea, and fatigue.
- *Thrombocytopenia*: petechiae, bruising, epistaxis, vaginal bleeding, and unexpected bleeding at other sites are frequently presenting signs of the underlying marrow disorder.
- *Neutropenia and monocytopenia*: this is a rare disease presentation and may be more dramatic with fever, chills, and pharyngitis or other sites of infection resulting from severe neutropenia and monocytopenia.

Physical Examination

Generally it is unrevealing except for evidence of anemia (e.g., conjunctival and cutaneous pallor, resting tachycardia) or cutaneous bleeding (e.g., ecchymoses and petechiae), gingival bleeding, and intraoral purpura.

Lymphadenopathy and splenomegaly are not features of aplastic anemia; such findings suggest an alternative diagnosis such as a clonal myeloid or lymphoid disease.

Laboratory Features

Blood Findings

Patients with aplastic anemia have varying degrees of *pancytopenia*:

- Anemia is associated with a low reticulocyte index.
- Absolute neutrophil and monocyte count are low. Lymphocyte production is thought to be normal, but patients may have mild lymphopenia.
- Platelets function normally.

Plasma Findings

Plasma contains high levels of hematopoietic growth factors:

- Erythropoietin
- TPO
- Myeloid colony-stimulating factors

Marrow biopsy is essential to confirm the overall hypocellularity. In severe aplastic anemia, as defined by the International Aplastic Anemia Study Group, less than 25% cellularity or less than 50% cellularity with less than 30% hematopoietic cells are seen in the marrow.

Natural History

The natural history of SAA is continued progression of cytopenias, with minimal chance of spontaneous remission. Clinical outcomes do correlate with severity at presentation—with a worse prognosis for very SAA. Moderate AA may spontaneously remit and may not require treatment [77].

Diagnosis

Measurement of the reticulocyte count and an examination of the blood film and marrow biopsy are essential early steps to arrive at a diagnosis.

A reticulocyte percentage of 0.5% to zero is strongly indicative of aplastic erythropoiesis. When coupled with leukopenia and thrombocytopenia, the diagnosis points to aplastic anemia.

The absence of qualitative abnormalities of cells on the blood film and a markedly hypocellular marrow are characteristic of acquired aplastic anemia.

Diagnosis requires the presence of *pancytopenia*:

- Neutrophil count fewer than 1500/μL (1.5×10^9/L)
- Platelet count fewer than 50,000/μL (50×10^9/L)
- Hemoglobin concentration less than 10 g/dL (100 g/L)
- Absolute reticulocyte count fewer than 40,000/μL (40×10^9/L)

Bone marrow evaluations including an aspirate and a biopsy are obligatory [77], accompanied by a *hypocellular marrow* without abnormal or malignant cells or fibrosis.

Differential Diagnosis

Any disease that can present with pancytopenia may mimic aplastic anemia if only the blood counts are considered.

The disorders most commonly confused with severe aplastic anemia include patients with myelodysplastic syndromes who present with a hypoplastic rather than a hypercellular marrow (approximately 5–10% of patients with myelodysplastic syndromes).

Differential diagnosis of acquired aplastic anemia includes:

- Hypoplastic marrow that can accompany paroxysmal nocturnal hemoglobinuria or hypoplastic oligoblastic (myelodysplastic syndrome)
- Polyblastic myelogenous leukemia

Treatment

Supportive Care

- Red blood cell transfusion
- Platelet transfusion
- Management of neutropenia

Immunosuppressive therapy or hematopoietic stem cell transplantation (HSCT) is the main treatment modality for severe aplastic anemia (SAA), based on patient's [76] age, availability of histocompatible siblings, and disease severity. The HSCT restores normal hematopoiesis and is accepted as the therapy of choice for SAA patients who have human leukocyte antigen (HLA)-matched donors. Although the survival rate has been improved, the major causes of failure after HSCT in SAA are graft-versus-host disease (GVHD), infection, and graft rejection [77].

Irrespective of the treatment method, longitudinal surveillance throughout life for development of late complications of marrow failure and its treatment is mandatory in these adolescents and young adults [78].

Specific treatment of the marrow aplasia involves two principal options:

1. Syngeneic or allogeneic hematopoietic stem cell transplantation
2. Combination immunosuppressive therapy (IST) with ATG and cyclosporine

Immunotherapy

Another highly effective therapy for SAA is antithymocyte globulin (ATG) and cyclosporine (CsA) IST. This is generally the first-line therapy for adolescent and young adult SAA patients who lack matched sibling donors [15] . The hematopoietic response rate after ATG/CsA is 60–70%, and the probability of survival at 5 years ranges from 60 to 85% [1] . However, up to 40% of patients eventually relapse, a significant concern in this age group with long life expectancy [78].

The disease may be significantly ameliorated or occasionally cured by immunotherapy, especially a regimen coupling antithymocyte globulin with cyclosporine. However, after successful treatment with immunosuppressive agents, the disease may relapse or evolve into a clonal myeloid disorder, such as paroxysmal nocturnal hemoglobinuria, a clonal cytopenia, or oligoblastic or polyblastic myelogenous leukemia.

Combination immunosuppressive therapy with ATG and cyclosporine leads to a marked improvement in approximately 70% of the patients.

Late Effects After Treatment

The most important nonmalignant late complications in AA are avascular necrosis of the bone, gonadal dysfunction with infertility, and cataracts [82].

Clonal outgrowth with secondary hematological malignancies and impaired fertility are among the most profound late effects of IST and HCT, respectively, for adolescents and young adults treated for AA. Patients treated with IST should be told that there is a 1–5% chance of secondary hematological malignancies with clonal evolution to MDS or clinical PNH. Routine monitoring (generally annual) should be performed [78].

Bone health and overall endocrine function must also be monitored over the long term [25]. After IST or HCT, hip or other persistent joint pain should prompt imaging to evaluate for avascular necrosis and appropriate orthopedic or physical therapy referral [77].

Monitoring for osteopenia may be appropriate if steroid use and/or inactivity have been prolonged or if there is endocrine dysfunction.

Serial thyroid monitoring should be implemented because as many as 10% of patients may have hypothyroidism after HCT.

Rates of both melanoma and nonmelanoma skin cancer are increased after IST and HCT. Renal dysfunction and hypertension have also emerged as treatment-related issues.

Evaluation for metabolic syndrome, which can be considered as a late treatment effect, is important [77].

Effect on Fertility and Fertility Preservation Options

Fear of infertility should not be considered a reason to withhold an HCT in a young patient. Both female and male survivors of matched sibling HCT for SAA have demonstrated fertility. The majority with successful reproduction after HCT received nonmyeloablative matched sibling HCT with ATG/cyclophosphamide [23]. While transient ovarian and testicular dysfunction are common after cyclophosphamide-based HCT preparative regimens for SAA, fertility can return over the longer term [24]. In those who receive myeloablative preparatory regimens, preserved fertility is much less likely [22]. Fertility preservation techniques such as semen, egg, or embryo cryopreservation should be attempted where possible and desired. Such attempts must weigh the planned conditioning regimen, the rapidity with which the move to HCT is anticipated, and any procedural complications due to risks of infection or bleeding. While they may or may not be at an age where this is a current concern, fertility issues should be discussed at length as limited options could later have significant social consequences. Monitoring for fertility after transplantation can be done as part of a survivorship program in consultation with reproductive endocrinologists [77].

Regardless of the treatment method in these adolescents and young adults, long-term follow-up for the development of late complications of the disease and treatment is mandatory.

Prognosis

Prognosis of patients with aplastic anemia (AA) treated with hematopoietic stem cell transplantation (HSCT) has greatly improved. Nevertheless, long-term morbidity may occur and can be responsible for the persistent increased death rates as compared to general population. Most late effects evolve during the first 10 years posttransplant; however, some of them may appear later. Patients with AA undergoing HSCT from a matched sibling donor (MSD) present a lower incidence of nonmalignant late complications when compared to patients transplanted for a malignant disease [81].

HSCT

HSCT is a curative therapy for tens of thousands of people yearly who are affected by a wide variety of marrow failure states, myeloid and lymphoid malignancies, immune deficiencies, and inborn errors of metabolism [8].

With the introduction of HSCT for nonmalignant conditions, there is now a curative treatment for these conditions. It is typically employed early in the course of the disease and at a younger age, before the onset of irreversible organ damage.

In the United States, survival during childhood has improved significantly due to better supportive care for children with TM and SCD [4, 5], but average life expectancy remains half that of the general population (40 years for a male with HbSS and 48 years for a female HbSS patient) [47, 82].

To date, the only curative therapy for both structural hemoglobinopathies and the thalassemias remains to be allogeneic hematopoietic stem cell transplantation (HSCT).

Successful hematopoietic cell transplantation (HCT) is curative for patients with hemoglobinopathy and able to prevent disease-/transfusion-related organ damage if the erythroid compartment is adequately replaced by donor-derived erythropoiesis, with event-free survival rates averaging 85–90% for allogeneic transplantations [83].

Although the intensity of preparatory myeloablation varies among conditions being treated with stem cell transplantation, chemotherapy in conjunction with TBI is typically performed as part of the immunosuppressive regime prior to BMT [84]. As reduced-intensity preparatory regimens for BMT continue to be developed, it is hoped that risk of gonadal dysfunction will decrease [46, 66].

Major Thalassemia

A minority of BTM patients who fulfill certain requirements are eligible to receive a curative bone marrow transplantation (BMT) [13]. BMT is the only way in which they can be cured, but it is limited to those patients with an appropriately matched donor [1]. Recent experience suggests that patients without matched donors could benefit from haploidentical mother-to-child transplantation.

Sickle Disease

Because SCD is an inherited defect in the hematopoietic stem cell, stem cell transplantation (SCT) is an attractive option to permanently cure the disease rather than managing its sequelae as HSCT aims to eradicate the underlying disorder by replacing the defective host hematopoietic cells with healthy donor ones. AHSCT should be done in patients who are likely to have a severe disease course, but should be instituted early, prior to end-organ damage.

Data on outcomes after matched sibling donor bone marrow transplantation in children with SCA show an overall survival of 95%; early or late allograft failure resulting in disease recurrence occurs in 10–15% of patients [45, 47].

AHSCT is an underused treatment modality in SCD even in eligible patients secondary to lack of donor availability and socioeconomic factors. Only 15–20% of

patients with SCD are able to identify an appropriately matched donor for possible HSCT.

Human leukocyte antigen (HLA)-matched sibling donor transplant with myeloablative conditioning represents the most common transplant type in SCD. Acute or chronic graft-versus-host disease, toxic effects of conditioning regimens, prolonged and severe cytopenias, susceptibility to infections in the posttransplantation period, and other adverse effects are commonly observed during HSCT. The overall frequency of mild to severe grades ranges from 27 to 30%. Some of these effects have been mitigated somewhat with the increasing use of nonmyeloablative conditioning regimens [1]. The risk-to-benefit ratio of the morbidity and mortality associated with AHSCT has to be weighed against the disease severity of a nonmalignant hematologic disorder.

The most common myeloablative regimen used is busulfan, cyclophosphamide, and antithymocyte globulin; the addition of antithymocyte globulin resulted in a significant reduction in allograft rejection. Transplant-related mortality ranges between 2 and 8%.

Acute graft-versus-host disease occurs in approximately 10–15% of patients, whereas chronic graft-versus-host disease has been reported in 12–20% of patients. Most series have used cyclosporine alone or in combination with methotrexate for graft-versus-host disease prophylaxis.

HCT from human leukocyte antigen (HLA)-matched sibling donors (MSD) following myeloablative conditioning (MAC) has high cure rates (>85%) even when the sibling donor carries a hemoglobinopathy trait. The preference for MAC is based upon increased rates of graft rejection (GR) noted with HCT following reduced-intensity and nonmyeloablative regimens. However, MAC is associated with short-term risks of organ toxicities, as well as late sequelae such as sterility. The immediate risks of GR, marrow aplasia, infection, graft-versus-host disease (GVHD), and transplant-related mortality (TRM) can delay the consideration of transplant until after disease sequelae have taken a toll. Long-term toxicity still remains a concern, especially in relation to growth, reproduction, and secondary malignancies. Follow-up data on AHSCT in children between 1991 and 2000 show significant gonadal toxicity and infertility, especially in females [45].

Resumption of normal menstrual cycles within a year of HCT in four teenagers was encouraging for the preservation of ovarian function, and continued monitoring is in progress. Three other female HCT recipients of the same RIC regimen for nonmalignant disorders have maintained fertility, indicating that preservation of ovarian function may be a viable possibility. Longer follow-up is necessary to determine whether the regimen is associated with male gonadal toxicity.

Graft rejection, GVHD, and transplantation-related mortality remain primary concerns, but other transplantation-related outcomes such as endocrine dysfunction and impaired fertility are important issues as well.

If the toxicity of conditioning regimens could be decreased while maintaining low rates of graft rejection, HSCT may be considered more often in patients with SCD before severe acute complications and major end-organ damage occur.

Myeloablative conditioning regimens before HSCT for SCD cause infertility, particularly in females [58]; due the unpredictable risk of infertility, patients may opt for procedures to preserve fertility before HSCT regardless of conditioning regimens.

Currently BMT is being pursued as a cure for SCA, but can be limited due to lack of an identifiable donor, and has many risks, including graft failure, graft-versus-host disease, and gonadotoxicity. Similarly, gonadotoxic effects are seen after BMT. Following BMT, studies suggest a high rate of gonadal failure in females and azoospermia in males.

Common preparatory regimen for BMT includes use of cyclophosphamide and busulfan, two alkylating agents whose use in pediatric cancer patients has been associated with infertility in males and females [66].

Chemotherapeutic agents can result in varying degrees of gonadal hypofunction, including diminished ovarian reserve (DOR) and/or premature ovarian insufficiency (POI). Published normative data regarding AMH levels, although limited, exist for the pediatric and adolescent populations [66].

Total Body Irradiation (TBI)

Human oocytes are extremely sensitive to ionizing radiation, and some commonly used chemotherapy agents are well known to be gonadotoxic. Direct radiation causes a dose-dependent and age-related reduction in the ovarian follicular pool. Patients having TBI therapy are particularly exposed to ovarian insufficiency with a risk of more than 80% [46].

Aplastic Anemia

The definitive treatment for a younger patient with a human leukocyte antigen (HLA)-identical sibling is an HCT. The cure rate for this younger cohort now approaches 90%, primarily due to advances in supportive care and standardization of conditioning regimens. In the absence of an HLA-identical sibling, IST is the most common alternative first-line approach to treatment [77].

The selection of the specific mode of treatment depends on several factors, including the patient's age and condition and the availability of a suitable allele-level HLA-matched hematopoietic stem cell donor.

In general, transplantation is the preferred treatment for children and most otherwise healthy younger adults. Early histocompatibility testing of siblings is of particular importance because it establishes whether there is an optimal donor available to the patient for transplantation. The preferred stem cell source is a histocompatible sibling matched at the HLA-A, HLA-B, HLA-C, and HLA-DR loci. ATG and

cyclophosphamide have been used as the preparative regimen for transplantation in aplastic anemia, as their use has markedly reduced the problem of graft rejection.

Severe aplastic anemia is the most common nonmalignant hematologic indication for hematopoietic cell transplantation, and transplantation is curative.

Survival after AHSCT for severe aplastic anemia has improved over time such that survival rates now approach 90% after HLA-matched sibling and 75% after HLA-matched unrelated donor bone marrow transplantation [3–6]. Several reports also support bone marrow as the preferred source of stem cells [7, 8]. Transplantation of peripheral blood progenitor cells from HLA-matched siblings and adult unrelated donors is associated with higher mortality rates secondary to a higher incidence of chronic graft-versus-host disease (GVHD) [1, 5, 9] [78].

Adolescents and young adults (age of <30 years) with SAA who have an HLA-matched sibling donor should proceed directly to HCT as this is potentially curative [77].

Prompt therapy usually is indicated for patients with severe aplastic anemia. The major curative approach is hematopoietic stem cell transplantation from a histocompatible sibling. Only 20–30% of patients in the United States have compatible sibling donors.

AHSCT is the principal treatment for young patients with severe aplastic anemia and available HLA-matched sibling donor.

The longer the delay between diagnosis and transplantation, the less likely is a salutary outcome, probably as a result of a greater number of transfusions and a higher likelihood of pretransplantation infection. Acute and chronic graft-versus-host disease are serious complications, and therapy to prevent or ameliorate them is a standard part of posttransplantation treatment [80].

AHSCT is curative in approximately 80% of younger patients with high-resolution human leukocyte antigen-matched sibling donors, although the posttransplant period may be complicated by severe graft-versus-host disease.

The rate of post-HSCT infertility is greatly influenced by the gonadotoxic potential of the conditioning regimen and the age of the patient at the time of transplantation [85].

Myeloablative pretransplant conditioning regimens are based on TBI and/or alkylating agents. Most patients treated with TBI experience early gonadal failure, and the reported incidence of pregnancy is less than 3% [85]. Myeloablative therapy using cyclophosphamide, busulfan, or melphalan has been suggested as an alternative approach to avoid the side effects of irradiation [85].

Younger age at the time of HSCT reduces the risk of immediate ovarian failure, but fertility will nevertheless be impaired over time.

The type of transplant (allogeneic versus autologous) or previous treatment with alkylating agents have not yet been shown to affect the prevalence of POI [85].

Overall pregnancy rates after HSCT remain low, ranging from 0.6 to 11% depending on study.

Pregnancies in women subjected to HSCT are likely to have successful outcomes in over 80% of cases, and there is no evidence of increased congenital abnormalities.

However, women undergoing TBI have higher rates of preterm deliveries, cesarean sections, and low birth weight babies especially if TBI was performed during childhood [85].

Because of the high risk of POI, it is mandatory to discuss fertility preservation options with women and girls requiring HSCT. Cryopreservation of embryos, oocytes, and ovarian tissue can be proposed [85].

References

1. Goodman MA, Malik P. The potential of gene therapy approaches for the treatment of hemoglobinopathies: achievements and challenges. Ther Adv Hematol. 2016;7(5):302–15.
2. Nouraie M, Lee JS, Zhang Y, Kanias T, Zhao X, Xiong Z, et al. The relationship between the severity of hemolysis, clinical manifestations and risk of death in 415 patients with sickle cell anemia in the US and Europe. Haematologica. 2013;98(3):464–72.
3. Fung EB, Harmatz P, Milet M, Ballas SK, De Castro L, Hagar W, et al. Morbidity and mortality in chronically transfused subjects with thalassemia and sickle cell disease: a report from the multi-center study of iron overload. Am J Hematol. 2007;82(4):255–65.
4. King AA, Kamani N, Bunin N, Sahdev I, Brochstein J, Hayashi RJ, et al. Successful matched sibling donor marrow transplantation following reduced intensity conditioning in children with hemoglobinopathies. Am J Hematol. 2015;90(12):1093–8.
5. Jackson JL, Lemanek KL, Clough-Paabo E, Rhodes M. Predictors of health-related quality of life over time among adolescents and young adults with sickle cell disease. J Clin Psychol Med Settings. 2014;21(4):313–9.
6. Boonchooduang N, Louthrenoo O, Choeyprasert W, Charoenkwan P. Health-related quality of life in adolescents with thalassemia. Pediatr Hematol Oncol. 2015;32(5):341–8.
7. King AA, Rodeghier MJ, Panepinto JA, Strouse JJ, Casella JF, Quinn CT, et al. Silent cerebral infarction, income, and grade retention among students with sickle cell anemia. Am J Hematol. 2014;89(10):E188–92.
8. Weatherall DJ. The thalassemias: disorders of globin synthesis. In: Kaushansky K, editor. Williams hematology, vol. 1. 9th ed. Newyork: McGraw-Hill; 2015.
9. Safari Moradabadi A, Alavi A, Eqbal Eftekhaari T, Dadipoor S. The reproductive behavior of families with thalassemic children in hormozgan. J Reprod Infertil. 2015;16(3):167–70.
10. Chernoff AI. The distribution of the thalassemia gene: a historical review. Blood. 1959;14(8):899–912.
11. Rund D, Oron-Karni V, Filon D, Goldfarb A, Rachmilewitz E, Oppenheim A. Genetic analysis of beta-thalassemia intermedia in Israel: diversity of mechanisms and unpredictability of phenotype. Am J Hematol. 1997;54(1):16–22.
12. Rund D, Fucharoen S. Genetic modifiers in hemoglobinopathies. Curr Mol Med. 2008;8(7):600–8.
13. Weidlich D, Kefalas P, Guest JF. Healthcare costs and outcomes of managing beta-thalassemia major over 50 years in the United Kingdom. Transfusion. 2016;56(5):1038–45.
14. Castaldi MA, Cobellis L. Thalassemia and infertility. Hum Fertil (Camb, Engl). 2016;19(2):90–6.
15. Siniscalco M, Bernini L, Filippi G, Latte B, Meera Khan P, Piomelli S, et al. Population genetics of haemoglobin variants, thalassaemia and glucose-6-phosphate dehydrogenase deficiency, with particular reference to the malaria hypothesis. Bull World Health Organ. 1966;34(3):379–93.
16. Weatherall DJ. Phenotype-genotype relationships in monogenic disease: lessons from the thalassaemias. Nat Rev Genet. 2001;2(4):245–55.

17. Wonke B, Hoffbrand AV, Bouloux P, Jensen C, Telfer P. New approaches to the management of hepatitis and endocrine disorders in Cooley's anemia. Ann N Y Acad Sci. 1998;850:232–41.
18. Choudhury NJ, Dubey ML, Jolly JG, Kalra A, Mahajan RC, Ganguly NK. Post-transfusion malaria in thalassaemia patients. Blut. 1990;61(5):314–6.
19. Morris CR, Kuypers FA, Kato GJ, Lavrisha L, Larkin S, Singer T, et al. Hemolysis-associated pulmonary hypertension in thalassemia. Ann N Y Acad Sci. 2005;1054:481–5.
20. Wood JC, Enriquez C, Ghugre N, Otto-Duessel M, Aguilar M, Nelson MD, et al. Physiology and pathophysiology of iron cardiomyopathy in thalassemia. Ann N Y Acad Sci. 2005;1054:386–95.
21. Ganz T, Nemeth E. Iron metabolism: interactions with normal and disordered erythropoiesis. Cold Spring Harb Perspect Med. 2012;2(5):a011668.
22. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood. 1997;89(3):739–61.
23. Multicentre study on prevalence of endocrine complications in thalassaemia major Italian working group on endocrine complications in non-endocrine diseases. Clin Endocrinol (Oxf). 1995;42(6):581–6.
24. Chatterjee R, Katz M, Cox TF, Porter JB. Prospective study of the hypothalamic-pituitary axis in thalassaemic patients who developed secondary amenorrhoea. Clin Endocrinol (Oxf). 1993;39(3):287–96.
25. Soliman A, Yasin M, El-Awwa A, Osman M, de Sanctis V. Acute effects of blood transfusion on pituitary gonadal axis and sperm parameters in adolescents and young men with thalassemia major: a pilot study. Fertil Steril. 2012;98(3):638–43.
26. De Sanctis V, Borsari G, Brachi S, Govoni M, Carandina G. Spermatogenesis in young adult patients with beta-thalassaemia major long-term treated with desferrioxamine. Georgian Med News. 2008;156:74–7.
27. Allegra A, Capra M, Cuccia L, Pulejo ML, Raineri L, Corselli F, et al. Hypogonadism in beta-thalassemic adolescents: a characteristic pituitary-gonadal impairment. The ineffectiveness of long-term iron chelation therapy. Gynecol Endocrinol : Off J Int Soc Gynecol Endocrinol. 1990;4(3):181–91.
28. Al-Rimawi HS, Jallad MF, Amarin ZO, Al SR. Pubertal evaluation of adolescent boys with beta-thalassemia major and delayed puberty. Fertil Steril. 2006;86(4):886–90.
29. Raiola G, Galati MC, De Sanctis V, Caruso Nicoletti M, Pintor C, De Simone M, et al. Growth and puberty in thalassemia major. J Pediatric Endocrinol Metab JPEM. 2003;16(Suppl 2):259–66.
30. Origa R, Piga A, Quarta G, Forni GL, Longo F, Melpignano A, et al. Pregnancy and beta-thalassemia: an Italian multicenter experience. Haematologica. 2010;95(3):376–81.
31. Singer ST, Sweeters N, Vega O, Higa A, Vichinsky E, Cedars M. Fertility potential in thalassemia major women: current findings and future diagnostic tools. Ann N Y Acad Sci. 2010;1202:226–30.
32. Thompson AA, Kim HY, Singer ST, Vichinsky E, Eile J, Yamashita R, et al. Pregnancy outcomes in women with thalassemia in North America and the United Kingdom. Am J Hematol. 2013;88(9):771–3.
33. Singer ST, Vichinsky EP, Gildengorin G, van Disseldorp J, Rosen M, Cedars MI. Reproductive capacity in iron overloaded women with thalassemia major. Blood. 2011;118(10):2878–81.
34. Tsironi M, Karagiorga M, Aessopos A. Iron overload, cardiac and other factors affecting pregnancy in thalassemia major. Hemoglobin. 2010;34(3):240–50.
35. Bajoria R, Chatterjee R. Current perspectives of fertility and pregnancy in thalassemia. Hemoglobin. 2009;33(Suppl 1):S131–5.
36. Skordis N, Petrikkos L, Toumba M, Hadjigavriel M, Sitarou M, Kolnakou A, et al. Update on fertility in thalassaemia major. Pediatr Endocrinol Rev PER. 2004;2(Suppl 2):296–302.
37. Rachmilewitz EA, Weizer-Stern O, Adamsky K, Amariglio N, Rechavi G, Breda L, et al. Role of iron in inducing oxidative stress in thalassemia: can it be prevented by inhibition of absorption and by antioxidants? Ann N Y Acad Sci. 2005;1054:118–23.

38. Roussou P, Tsagarakis NJ, Kountouras D, Livadas S, Diamanti-Kandarakis E. Beta-thalassemia major and female fertility: the role of iron and iron-induced oxidative stress. Anemia. 2013;2013:617204.
39. Gluckman E. Allogeneic transplantation strategies including haploidentical transplantation in sickle cell disease. Hematology Am Soc Hematol Educ Program. 2013;2013:370–6.
40. Ruggeri A, Eapen M, Scaravadou A, Cairo MS, Bhatia M, Kurtzberg J, et al. Umbilical cord blood transplantation for children with thalassemia and sickle cell disease. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2011;17(9):1375–82.
41. Bolanos-Meade J, Fuchs EJ, Luznik L, Lanzkron SM, Gamper CJ, Jones RJ, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood. 2012;120(22):4285–91.
42. Cheung MC, Goldberg JD, Kan YW. Prenatal diagnosis of sickle cell anaemia and thalassaemia by analysis of fetal cells in maternal blood. Nat Genet. 1996;14(3):264–8.
43. Hung EC, Chiu RW, Lo YM. Detection of circulating fetal nucleic acids: a review of methods and applications. J Clin Pathol. 2009;62(4):308–13.
44. Kuliev A, Rechitsky S, Verlinsky O, Ivakhnenko V, Evsikov S, Wolf G, et al. Preimplantation diagnosis of thalassemias. J Assist Reprod Genet. 1998;15(5):219–25.
45. Natrajan K, Abdullah Kutlar,et al. Disorders of hemoglobin structure: sickle cell anemia and related abnormalities. In: Kaushansky K, editor. Williams Hematology.9ed. 1. New York: McGraw-Hill; 2015.
46. Lavery SA, Islam R, Hunt J, Carby A, Anderson RA. The medical and ethical challenges of fertility preservation in teenage girls: a case series of sickle cell anaemia patients prior to bone marrow transplant. Hum Reprod. 2016;31(7):1501–7.
47. Meier ER, Dioguardi JV, Kamani N. Current attitudes of parents and patients toward hematopoietic stem cell transplantation for sickle cell anemia. Pediatr Blood Cancer. 2015;62(7):1277–84.
48. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. Am J Med. 2009;122(6):507–12.
49. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med. 2011;41(6 Suppl 4):S398–405.
50. Yale SH, Nagib N, Guthrie T. Approach to the vaso-occlusive crisis in adults with sickle cell disease. Am Fam Physician. 2000;61(5):1349–56. 63-4
51. Kinney TR, Ware RE, Schultz WH, Filston HC. Long-term management of splenic sequestration in children with sickle cell disease. J Pediatr. 1990;117(2 Pt 1):194–9.
52. Ballas SK, Kesen MR, Goldberg MF, Lutty GA, Dampier C, Osunkwo I, et al. Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. ScientificWorldJournal. 2012;2012:949535.
53. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. Am Heart J. 1972;83(3):415–26.
54. Stockman JA, Nigro MA, Mishkin MM, Oski FA. Occlusion of large cerebral vessels in sickle-cell anemia. N Engl J Med. 1972;287(17):846–9.
55. Nur E, Biemond BJ, Otten HM, Brandjes DP, Schnog JJ. Oxidative stress in sickle cell disease; pathophysiology and potential implications for disease management. Am J Hematol. 2011;86(6):484–9.
56. Mantadakis E, Cavender JD, Rogers ZR, Ewalt DH, Buchanan GR. Prevalence of priapism in children and adolescents with sickle cell anemia. J Pediatr Hematol/Oncol. 1999;21(6):518–22.
57. Smith-Whitley K. Reproductive issues in sickle cell disease. Blood Cells Mol Dis. 2014;124(24):3538–43.
58. Luban NL, Leikin SL, August GA. Growth and development in sickle cell anemia. Preliminary report. Am J Pediatr Hematol/Oncol. 1982;4(1):61–5.

59. Zemel BS, Kawchak DA, Ohene-Frempong K, Schall JI, Stallings VA. Effects of delayed pubertal development, nutritional status, and disease severity on longitudinal patterns of growth failure in children with sickle cell disease. Pediatr Res. 2007;61(5 Pt 1):607–13.
60. Taddesse A, Woldie IL, Khana P, Swerdlow PS, Chu JW, Abrams J, et al. Hypogonadism in patients with sickle cell disease: central or peripheral? Acta Haematol. 2012;128(2):65–8.
61. Dada OA, Nduka EU. Endocrine function and haemoglobinopathies: relation between the sickle cell gene and circulating plasma levels of testosterone, luteinising hormone (LH) and follicle stimulating hormone (FSH) in adult males. Clin Chim Acta Int J Clin Chem. 1980;105(2):269–73.
62. Berthaut I, Guignedoux G, Kirsch-Noir F, de Larouziere V, Ravel C, Bachir D, et al. Influence of sickle cell disease and treatment with hydroxyurea on sperm parameters and fertility of human males. Haematologica. 2008;93(7):988–93.
63. Osegbe DN, Akinyanju O, Amaku EO. Fertility in males with sickle cell disease. Lancet (London, England). 1981;2(8241):275–6.
64. Fung EB, Harmatz PR, Lee PD, Milet M, Bellevue R, Jeng MR, et al. Increased prevalence of iron-overload associated endocrinopathy in thalassaemia versus sickle-cell disease. Br J Haematol. 2006;135(4):574–82.
65. National Toxicology Program. NTP-CERHR monograph on the potential human reproductive and developmental effects of hydroxyurea. NTP CERHR MON. 2008;21:vii–viii., v, ix-III1
66. Elchuri SV, Williamson RS, Clark Brown R, Haight AE, Spencer JB, Buchanan I, et al. The effects of hydroxyurea and bone marrow transplant on Anti-Mullerian hormone (AMH) levels in females with sickle cell anemia. Blood Cells Mol Dis. 2015;55(1):56–61.
67. Lukusa AK, Vermylen C, Vanabelle B, Curaba M, Brichard B, Chantrain C, et al. Bone marrow transplantation or hydroxyurea for sickle cell anemia: long-term effects on semen variables and hormone profiles. Pediatr Hematol Oncol. 2009;26(4):186–94.
68. Lukusa AK, Vermylen C. Use of hydroxyurea from childhood to adult age in sickle cell disease: semen analysis. Haematologica. 2008;93(11):e67. ; discussion e8.
69. Ginsberg JP, Li Y, Carlson CA, Gracia CR, Hobbie WL, Miller VA, et al. Testicular tissue cryopreservation in prepubertal male children: an analysis of parental decision-making. Pediatr Blood Cancer. 2014;61(9):1673–8.
70. Jadoul P, Dolmans MM, Donnez J. Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed? Hum Reprod Update. 2010;16(6):617–30.
71. Practice Committees of American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013;99(1):37–43.
72. Dovey S, Krishnamurti L, Sanfilippo J, Gunawardena S, McLendon P, Campbell M, et al. Oocyte cryopreservation in a patient with sickle cell disease prior to hematopoietic stem cell transplantation: first report. J Assist Reprod Genet. 2012;29(3):265–9.
73. Donnez J, Silber S, Andersen CY, Demeestere I, Piver P, Meirow D, et al. Children born after autotransplantation of cryopreserved ovarian tissue. a review of 13 live births. Ann Med. 2011;43(6):437–50.
74. Quinn GP, Stearsman DK, Campo-Engelstein L, Murphy D. Preserving the right to future children: an ethical case analysis. Am J Bioeth AJOB. 2012;12(6):38–43.
75. Brawley OW, Cornelius LJ, Edwards LR, Gamble VN, Green BL, Inturrisi C, et al. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. Ann Intern Med. 2008;148(12):932–8.
76. Lee YH, Kim JY, Choi BO, Ryu MR, Chung SM. Total lymphoid irradiation based conditioning for hematopoietic stem cell transplantation in severe aplastic anemia. Radiat Oncol J. 2012;30(4):165–72.
77. DeZern AE, Guinan EC. Aplastic anemia in adolescents and young adults. Acta Haematol. 2014;132(3–4):331–9.

78. Eckrich MJ, Ahn KW, Champlin RE, Coccia P, Godder K, Horan J, et al. Effect of race on outcomes after allogeneic hematopoietic cell transplantation for severe aplastic anemia. Am J Hematol. 2014;89(2):125–9.
79. Williams DA, Bennett C, Bertuch A, Bessler M, Coates T, Corey S, et al. Diagnosis and treatment of pediatric acquired aplastic anemia (AAA): an initial survey of the North American Pediatric Aplastic Anemia Consortium (NAPAAC). Pediatr Blood Cancer. 2014;61(5):869–74.
80. Segel GB, Lichtman MA. Aplastic anemia: acquired and inherited. In: Kaushansky K, editor. Williams hematology. 1. 9th ed. New York: McGraw-Hill; 2015.
81. Tichelli A, Rovo A. Long-term outcome after hematopoietic stem cell transplant in patients with aplastic anemia. Curr Drug Targets. 2016.
82. Locatelli F, Kabbara N, Ruggeri A, Ghavamzadeh A, Roberts I, Li CK, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood. 2013;122(6):1072–8.
83. Michlitsch JG, Walters MC. Recent advances in bone marrow transplantation in hemoglobinopathies. Curr Mol Med. 2008;8(7):675–89.
84. Resetkova N, Hayashi M, Kolp LA, Christianson MS. Fertility preservation for prepubertal girls: update and current challenges. Curr Obstet Gynecol Rep. 2013;2(4):218–25.
85. Jadoul P, Kim SS, Committee IP. Fertility considerations in young women with hematological malignancies. J Assist Reprod Genet. 2012;29(6):479–87.

Chapter 6
Genetic Disorders Associated with Gonadal Dysfunction

Ataxia-Telangiectasia

Incidence

Ataxia-telangiectasia (A-T) has a frequency of approximately 1 in 40,000 births in the United States [1].

The carrier rate of A-T, which is an autosomal recessive genetic condition, is approximately 2.8% in the United States [2].

Natural History

A-T is an inherited genetic condition caused by pathogenic variants in *ATM*. *ATM* encodes the ATM protein kinase, which mobilizes cellular response to double-strand breaks in DNA by phosphorylating numerous DNA damage response (DDR) players. When both copies of *ATM* have a pathogenic mutation, the cell's ability to repair DNA damage is impaired. This leads to degeneration of specific tissues—particularly the nervous and immune systems. It is unknown why absence of ATM protein kinase leads to a slowly progressive disease with a variable phenotype rather than a more severe phenotype; however, it may have to do with the redundancy between ATM protein kinase and its close relative, the protein kinase ATR [3].

Disease Presentation

A-T has a complex and variable phenotype that affects several body systems and tissues. The primary characteristics of A-T include:

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_6

- Progressive neuronal degeneration
- Telangiectasias
- Immunodeficiency
- Cancer predisposition
- Acute sensitivity to ionizing radiation
- Gonadal dysfunction

Neurological symptoms: A-T is characterized by progressive neurodegeneration, which primarily affects the cerebellum. When a child with A-T begins to walk (approximately age 2–3 years), truncal ataxia is generally present. The ataxia subsequently spreads to affect the extremities, followed by speech. By the end of their first decade of life, children with A-T are typically wheelchair dependent [1, 3].

Mental status: In most cases, individuals with A-T have normal intellectual abilities. Many individuals with A-T complete university-level education [4].

Telangiectasias: Individuals with A-T typically have telangiectasias (dilated blood vessels), which appear variably in the ocular sclerae and occasionally in the facial skin and ears [1, 3].

Immunodeficiency: Individuals with A-T usually develop primary immunodeficiency, affecting the humoral and cellular systems of the body. Immunodeficiency causes a predisposition to infections, particularly sinopulmonary infections [1, 3].

Cancer predisposition: Approximately 1/3 of individuals with A-T develop a malignancy. The most common malignancies among individuals with A-T are lymphoma and leukemia. Younger children tend to develop common acute lymphocytic leukemia, while older individuals are prone to nonlymphoid cancers, such as the stomach, breast, basal cell, ovarian, liver, uterine, and melanoma. The predisposition to develop malignancies is complicated by the fact that conventional doses of radiation therapy and chemotherapy with radiomimetic agents are associated with adverse and sometimes fatal reactions in individuals with A-T [5].

Sensitivity to radiation: individuals with A-T are sensitive to the cytotoxic effect of ionizing radiation, which leads to chromosomal instability [3].

Secondary complications: The secondary complications of progressive ataxia include deconditioning/immobility, weight loss or gain, skin breakdown, recurrent pulmonary and urinary tract infections, aspiration, occult respiratory failure, and obstructive sleep apnea [4].

Life expectancy: Life expectancy for individuals with A-T varies but can be as late as the sixth decade of life. The three main causes of death are malignancy, infection, and nonspecific pulmonary failure [4].

Disease Management

There is no effective way stop the progressive ataxia associated with A-T. Treatment is symptom based and often includes managing the immunodeficiencies, sinopulmonary infections, neurologic dysfunction, and malignancy. Individuals with A-T usually receive physical, occupational, and speech/swallowing therapy.

Medications can be taken to improve balance, coordination, and dysarthria.

Supportive interventions, such as disease education, genetic counseling, individual and family counseling, referral to support groups and advocacy groups, as well as guidance to online resources, are recommended [4].

A-T Carriers and Cancer Susceptibility

The carrier rate for A-T in the United States is approximately 2.8% [2]. Carriers of A-T have increased cancer susceptibility compared to the general population, although this risk has been debated. Many studies have analyzed the association between cancer risk and A-T heterozygote status.

Morrell et al. (1990) measured the cancer incidence in 574 close relatives of individuals with A-T and 213 spouse controls from 44 previously unreported A-T families. They found that the relative risk of cancer in heterozygous carriers of A-T to be 6.1 compared to the non-carriers. The most frequent site of cancer in the carriers was the breast. Therefore, there may be an increased risk of developing breast cancer in A-T carriers [6].

Athma et al. (1996) analyzed breast cancer diagnoses in the United States and found that 6.6% may occur in women who are A-T carriers. Therefore, A-T carriers may be at greater risk than the general population to develop breast cancer [7].

Easton (1994) found that 8% of breast cancers in women under age 40 years occur in women who are A-T carriers, compared to 2% of breast cancers in women between age 50 and 59 years. This suggests that A-T carrier status is associated with an increased early-onset breast cancer risk [8].

FitzGerald et al.'s (1997) findings contradict previous studies by concluding heterozygous ATM pathogenic variants (found in A-T carriers) do not increase susceptibility to early onset of breast cancer. However, future studies were in agreement with previous studies, suggesting there is an increased early-onset breast cancer susceptibility associated with A-T carrier status [9].

Broeks et al. (2000) found the risk of developing breast cancer characterized by frequent bilateral occurrence, early age of onset, and long-term survival is nine times greater in A-T carriers than the general population. Therefore, women with heterozygous *ATM* pathogenic variants have an increased risk to develop young-onset breast cancer and survive following treatment [10].

Renwick et al. (2006) sought to further quantify the relative risk of developing breast cancer in A-T carrier by screening individuals from 443 familial breast cancer families and 531 controls for ATM pathogenic variants. They concluded that ATM mutations do confer breast cancer susceptibility in A-T carriers with an estimated relative risk of 2.37 [11].

Due to the increased risk of developing early-onset bilateral breast cancer and increased long-term survival, carriers of A-T may be interested in preserving their fertility prior to cancer treatment or prophylactic cancer risk reducing surgery. It is important to note that many A-T carriers may be identified in absence of family

history after the diagnosis of A-T in a child within the family. Genetic counseling is recommended to help explain the implications of A-T carrier status.

Effect on Fertility

Individuals with A-T are at risk for gonadal dysfunction. The following have all been reported in individuals with A-T:

- Hypogonadism
- Absent or hypoplastic ovaries/testes
- Ovarian dysgerminoma
- Infertility [12]

Zadik, et al. (1978) analyzed gonadal dysfunction in two males and three females diagnosed with A-T between ages 4 and 23 years. All five individuals had elevated basal levels of FSH, and three individuals had elevated levels of LH. The pubertal and adult females had low basal levels of estradiol. The laboratory and clinical findings of all five patients indicated primary gonadal failure is a characteristic of A-T [13].

In addition to risk of gonadal dysfunction, approximately 33% of individuals with A-T develop a malignancy [2]. Gonadotoxic drugs, such as chemotherapy, and/or total body irradiation (TBI) are typically used to treat malignancies; however, they may have harmful effects on fertility. Fertility preservation discussion is recommended among all individuals with A-T pathogenic variants. Additionally, due to the inherited nature of this disorder, individuals may be interested in pursuing preimplantation genetic diagnosis (PGD) in conjunction with fertility preservation.

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)

Prevalence

Fragile X syndrome, the most common heritable form of intellectual disability in males, affects approximately 1/4000 males [14]. It occurs in most ethnic and racial populations, but incidence may vary from group to group [15].

Fragile X syndrome is an X-linked genetic disorder caused by the presence of a mutation, specifically a trinucleotide repeat of increased size, in the *FMR1* gene. Female carriers may pass the mutation on to their children. Male children are expected to have the physical and behavioral features of fragile X syndrome. Some females with one copy of the mutation have been reported to have features of the condition but with lower frequency and often less severe symptoms.

Women who carry a fragile X premutation are at increased risk to develop fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS). In the largest US study to date (>119,000 women), the overall carrier frequency of fragile X among US females was found to be 1.3% [16].

Among women with primary ovarian insufficiency (POI), between 4 and 6% are fragile X carriers [17].

Natural History

The *FMR1* gene, located on the X chromosome, was identified in 1991 and was found to include a CGG trinucleotide repeat within the first exon (coding region). Expansion of this trinucleotide repeat leads to a group of disorders: fragile X, fragile X-associated primary ovarian insufficiency (FXPOI), and fragile X-associated tremor/ataxia syndrome (FXTAS). The size of the repeat correlates with the disorders an individual is at risk to develop, as detailed in Table 6.1 below [18].

The distinction between intermediate and premutation alleles is made by family history and repeat instability. Premutation alleles are unstable, and at risk to expand to a full mutation (>200 repeats) is some offspring. In contrast, intermediate alleles are not known to expand to full mutations; therefore, offspring are not at risk for fragile X syndrome. However, approximately 14% of intermediate alleles are unstable and may expand into the premutation range when transmitted by the mother [19]. To date, no allele 56 repeats or smaller has been known to expand to a full mutation in one generation [20].

It is important to note that the presence of AGG interruptions within the CGG trinucleotide repeat reduces the risk of transmission of a full mutation for all maternal premutation repeat lengths below ~100 CGG repeats [21].

Diagnosis

Fragile X syndrome carrier status is often diagnosed by one of the following three methods:

Table 6.1 *FMR1* CGG trinucleotide repeat size and associated classification and effect

Repeat size	Classification	Effect
5–44 repeats	Normal allele	No effect
45–54 repeats	Intermediate allele	No effect
55–200 repeats	Premutation allele	Increased risk for FXPOI among women and FXTAS among men and women
>200 repeats	Full mutation	Fragile X syndrome

- Evaluation for cause of POI
- Cascade testing when a family member is found to have fragile X syndrome, FXPOI, or FXTAS
- Preconception or prenatal carrier testing

Disease Presentation

Fragile X Syndrome

Fragile X syndrome is characterized by mental retardation or cognitive impairment. The degree of severity ranges from borderline, including learning disabilities, to severe. Fragile X syndrome may also present with behavioral disabilities, including autism [18, 22, 23]. Physical differences include distinctive facial features (long narrow face, prominent ears), macroorchidism, connective tissue problems, and speech and language difficulties [22].

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

Male and female *FMR1* premutation carriers are at increased risk to develop FXTAS, a late-onset neurodegenerative disorder characterized by progressive cerebellar ataxia, intention tremor, memory loss, anxiety, reclusive behavior, and dementia. Onset is typically after age 50 years and is more common in male carriers than female. Risk and severity are directly related to the size of the premutation repeat [18, 24].

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)

Women with *FMR1* premutations are at an approximate tenfold increased risk (~20%) of developing premature ovarian insufficiency (POI) or premature ovarian failure (POF)—diagnosed by amenorrhea and postmenopausal levels of follicle-stimulating hormone (FSH) before the age of 40 years [25, 26]. The risk of POI is dependent on the number of CGG repeats, with peak risk of POI at 80–100 repeats [27]. Women with full mutation alleles are not at increased risk for POI.

Effect on Fertility

Approximately 20% of female *FMR1* premutation carriers develop POI, defined as cessation of menses before age 40 years [26]. Of those who develop FXPOI, 1/3 will experience final cessation of menses at or before age 29 years, and 1% will have cessation of menses prior to age 18 years [27]. In fact, approximately 3% of

adolescents with *FMR1* premutations reportedly experience some menstrual cycle irregularity [27].

Additional Family Planning Considerations

While premutation carriers do not have fragile X syndrome, they are at increased risk to pass on a full mutation to their children. The likelihood of a carrier mother passing the full mutation to her children increases with the size of her premutation repeat allele, especially if she has at least 100 CGG repeats in the *FMR1* gene [19]. It is recommended that women with *FMR1* premutations (as well as intermediate mutations and full mutations) receive genetic counseling to discuss family planning options, including the availability of preimplantation genetic diagnosis (PGD) and prenatal diagnostic testing (amniocentesis and chorionic villus sampling (CVS)).

Emotional Well-Being

The diagnosis of POI can be devastating to young women who may not have completed, or even started, family planning. It is well established that loss of fertility can lead to emotional distress and women with *FMR1* premutations may be at increased risk for depression and anxiety. It is recommended that women with *FMR1* premutations receive a follow-up visit to screen for symptoms of depression and anxiety [28].

Fragile X Carrier Testing

The American College of Medical Genetics (ACMG) has issued a policy statement recommending fragile X testing for "women with reproductive or fertility problems associated with elevated FSH levels, especially if there is a family history of premature ovarian failure, fragile X syndrome, or undiagnosed mental retardation" [18, 29]. The Genetics Committee of the American College of Obstetrics & Gynecology supports the ACMG recommendation [22].

Galactosemia

Prevalence

Galactosemia affects between1:16,000 and 1:60,000 individuals [30, 31].

Natural History

Classic galactosemia is an autosomal recessive inherited metabolic disorder caused by deficient activity of galactose-1-phosphate uridyltransferase (GALT), as a result of pathogenic variants in the *GALT* gene. GALT is the second of three enzymes in the Leloir pathway—the main pathway of galactose metabolism.

Galactose is needed for energy metabolism and glycosylation of complex molecules. It can be derived two ways: either from exogenous (dietary) sources like lactose from dairy products or by endogenous production. A deficiency of GALT enzyme leads to accumulation of galactose and its metabolites in the body and results in secondary glycosylation abnormalities [32].

Almost all infants born in the United States with galactosemia are diagnosed through state newborn screening programs.

Disease Presentation

The symptoms of galactosemia present during the first few weeks of life with signs of liver and renal disease, cataracts, and *Escherichia coli* sepsis. A galactose-restricted diet resolves the early signs of galactosemia, but it cannot prevent development of later-onset complications, such as:

- Cognitive impairment
- Neurological sequelae
- Bone health abnormalities
- Primary ovarian insufficiency (POI) with subsequent infertility [32]

Effect on Fertility

Almost every female with classic galactosemia develops primary ovarian insufficiency (POI) as a diet-independent complication of the disease [33]. POI can vary from subfertility to early development of irregular menstrual cycles and infertility to primary amenorrhea and absence of spontaneous puberty. The mechanisms causing ovarian dysfunction are unknown. Postulated mechanisms of ovarian dysfunction include:

- Direct toxicity of metabolites (i.e., galactose-1-phosphate)
- Altered gene expression
- Aberrant function of hormone and/or receptors due to glycosylation abnormalities [32]

In general, POI is either caused by formation of a smaller primordial follicle pool or more rapid loss of primordial follicles [32]. Evidence of both has been

seen in individuals with galactosemia. Neonates have been reported with morphologically normal ovaries with abundant oocytes and normal folliculogenesis [34, 35]. Adolescents (16–17 years of age) have histological findings showing strongly reduced number of follicles, varying from far fewer follicles than expected for age to almost complete absence [36–38]. Additionally, patients ages 9–21 years were found by ultrasound or laparoscopy/laparotomy to have hypoplastic or streak ovaries [37–39].

It is possible that a normal complement of primordial follicles forms but undergoes atresia more rapidly and that the ovaries can be severely damaged in girls at very young prepubertal ages [32].

Spontaneous Pregnancy

Spontaneous pregnancies do occur in classic galactosemia, demonstrating that conception is possible in some affected females [32]. It is important to educate patients about the occurrence of spontaneous pregnancies, allow them to try to conceive spontaneously, and avoid unplanned pregnancies. Gubbels et al. (2008) had a cohort of 22 patients with classic galactosemia and POI. Nine patients in the cohort tried to conceive and four succeeded, resulting in a 44% success rate. The small sample size warrants further studies in larger cohorts. Additionally, it is important to note that most of the women who became pregnant spontaneously had gone through normal puberty and reached menarche spontaneously, indicating that these may be predictive factors for an increased chance of spontaneous conception [40, 41].

Expert Opinion

van Erven et al. (2013) has published the following recommendations based on expert opinion regarding fertility preservation in female classic galactosemia patients:

- Health care providers should emphasize that spontaneous pregnancies occur in women with classic galactosemia, even after POI diagnosis.
- If fertility preservation is desired, cryopreservation at an early prepubertal age as part of approved research currently seems to be the best option.
- The ethics committee of the hospital or another independent body should review the parent's decision before the fertility preservation procedure.
- The ethics committee of the hospital or another independent body should be involved in the decision-making surrounding the use of the cryopreserved material.
- If a patient desires pregnancy, a one-year window for attempting spontaneous pregnancy is advised to avoid unnecessary use of assisted reproductive techniques.

- Anonymous or intrafamilial oocyte donation might be another option for classic galactosemia patients if pregnancy does not occur spontaneously [32].

GAPO Syndrome

GAPO syndrome is a rare autosomal recessive genetic disorder characterized by growth retardation, alopecia, pseudoanodontia, and optic atrophy [42–44]. It is caused by pathogenic variants in *ANTXR1*, an anthrax toxin receptor gene. GAPO syndrome has been suggested to cause premature ovarian insufficiency in affected females. A histopathological study of the ovaries of a woman with GAPO syndrome and hypergonadotropic hypogonadism revealed follicular depletion [45]. Affected females may be interested in fertility preservation if at risk for infertility.

22q11.2 Deletion Syndrome[1]

Prevalence

22q11.2 deletion syndrome, also referred to as DiGeorge syndrome and velocardiofacial syndrome, is one of the most common genetic syndromes with a prevalence quoted between 1:3000 and 1:4000 [46]. Of the approximate 2.5 million children born each year in the United States, it is estimated that around 500–750 new cases of 22q11.2 deletion syndrome will be identified yearly [47].

Natural History

22q11.2 deletion syndrome is caused by a 1.5–3 Mb hemizygous deletion of chromosome 22q11.2. Chromosome 22 has been found to possess a high number of low-copy-number repeats, which suggests responsibility for the instability of 22q11. In a majority of cases of 22q11.2 deletion syndrome, the deletion is mediated by homologous recombination between regions of low-copy-number repeats [48, 49]. Within the 22q11.2 deletion region is *TBX1*, a key gene for vertebrate development. Haploinsufficiency of *TBX1* is responsible for major phenotypes that are seen among individuals with 22q11.2 deletion syndrome. However, the variability of phenotypic features with a deletion of *TBX1* suggests that altered interaction with downstream genes and environmental effects also affect the disease presentation [50]. As in all microdeletion syndromes, inheritance is autosomal dominant; however, most cases of 22q11.2 deletion syndrome result from a de novo or new, not inherited, microdeletion [46].

[1] (Contributions from Joanna Lee, MS, CGC).

Diagnosis

22q11.2 deletion syndrome is commonly diagnosed prenatally. Current indications for prenatal testing for 22q11.2 deletion syndrome include a previous child with a chromosome 22q11.2 deletion; even though the recurrence risk may be low, there is a possibility for germline mosaicism, an affected parent with a 22q11.2 deletion, or a visible congenital heart defect seen on a prenatal ultrasound [51]. If a congenital heart defect, most commonly a conotruncal cardiac defect, is seen on prenatal ultrasound or echocardiogram, information about family history is typically requested, specifically the presence of 22q11.2 deletion syndrome or a minimal phenotype, such as velopharyngeal insufficiency (VPI). An amniocentesis for FISH analysis at locus 22q11.2 would be performed to make a diagnosis [52]. An alternative to diagnostic amniocentesis is noninvasive prenatal screening (NIPS) by next-generation sequencing of cell-free DNA (cfDNA) in maternal plasma for presence of a 22q11.2 deletion. NIPS can screen for fetal genomic microdeletions, like 22q11.2 deletions [53–55]. It is important to note that NIPS is not a diagnostic test. Confirmation of results by amniocentesis or postnatal testing is recommended.

Postnatal diagnosis of 22q11.2 deletion syndrome is generally straightforward. A majority of patients with a clinical phenotype of 22q11.2 deletion syndrome have a hemizygous deletion of chromosome22q11.2. At this time, the most common and accurate method of diagnosis is fluorescence in situ hybridization (FISH) analysis; however, this method can be expensive. Multiplex ligation-dependent probe amplification (MLPA) testing has a relatively low cost and is a suitable screening method for 22q11.2 deletion syndrome. It includes the determination of the deletion breakpoints in a quantitative method. Additionally, chromosomal microarray can also identify 22q11.2 deletions. If a patient presents with clinical characteristics suggestive of 22q11.2 deletion syndrome, however no deletion is identified by FISH, MLPA, or chromosomal microarray analysis, there is a possibility of a point mutation in *TBX1*. As stated above, pathogenic variants in *TBX1* are typically undetectable by FISH, MLPA, or chromosomal microarray [50, 56].

Disease Presentation

22q11.2 deletion syndrome has many associated health problems that can affect almost every region of the body in an affected individual. Features can vary widely among affected individuals, even those from the same family. The most common findings include [46]:

- Heart anomalies (80% of patients)
- Frequent infections due to immunodeficiency/T-cell deficiency
- Developmental delay including speech delay, learning disabilities, and delayed growth

- Hypocalcaemia, which can lead to seizures—beginning in the neonatal period
- Cleft palate
- Distinctive facial features
- Increased risk of psychiatric disease, including schizophrenia
- Higher likelihood of ADHD and autism spectrum disorders
- Thymic aplasia or hypoplasia
- Gastrointestinal manifestations including feeding difficulties

Although not as common, it is important to note that six cases of females with 22q11.2 deletion syndrome have been reported to have uterovaginal aplasia [57].

Effect on Fertility

Uterovaginal aplasia, or Mayer–Rokitansky–Kuster–Hauser syndrome, has been associated with females with 22q11.2 deletion syndrome and causes the vagina and uterus to be underdeveloped or absent. Although affected females have a normal female karyotype (46, XX) and will develop normal secondary sex characteristics, they will not begin a menstrual period or be able to carry a pregnancy [57].

22q11.2 deletion syndrome patients without immunodeficiency may not be at any increased for infertility. However, individuals with 22q11.2 deletion syndrome and associated immunodeficiency due a T-cell deficiency may have fertility concerns related to a possible absent thymus gland [58]. Infants with 22q11.2 deletion syndrome and immunodeficiency can be broken down into two categories:

1. Infants with very low T-cell numbers and no skin rash present are classified as typical complete DiGeorge syndrome.
2. Infants, who develop oligoclonal T-cell populations associated with rash and lymphadenopathy, are classified as having atypical complete DiGeorge syndrome.

This distinction is important with respect to thymus transplantation because T cells in an atypical complete DiGeorge anomaly can reject transplantation [58].

For individuals with complete DiGeorge anomaly, transplantation of allogeneic postnatal cultured thymus has been successfully studied. Thymus transplants in both typical and atypical complete DiGeorge anomalies resulted in functional immune reconstitution. This was shown by diverse T-cell repertoires and good proliferative function in T cells [58]. Although the goal to prevent infection and therefore increase life span among 22q11.2 deletion syndrome patients is improving, thymus transplantation requires the use of immunosuppressant drugs, to prevent transplant rejection. Unfortunately, immunosuppressant drugs can cause infertility in both men and women. Families of children with 22q11.2 deletion syndrome who require transplantation should be informed of fertility preservation options prior to therapy initiation, allowing them to fully consider the options available for their child.

Additional Family Planning Considerations

Males and females with 22q11.2 deletion syndrome have a 50% chance with each pregnancy to pass the 22q11.2 deletion on to their offspring. Although prenatal testing is available, this can pose very difficult decisions for parents who have an affected pregnancy, as the topic of termination is a controversial one [59]. Geneticists and genetic counselors are important in the family planning decision-making process in order to fully inform families of their options prior to conception.

One alternative to prenatal testing is preimplantation genetic diagnosis (PGD). PGD makes it possible for to analyze embryos for specific genetic disorders. This process is completed in conjunction with in vitro fertilization and can therefore be quite costly.

The first case of PGD in a patient with 22q11.2 deletion syndrome was reported in 1998 by Iwarsson et al. (1998). The proband was a 31-year-old female with no clinical symptoms of DiGeorge syndrome but did present with the classic facial features. She received her diagnosis after the birth of a severely affected child, with a 22q11.2 deletion, who died at 4 months of age. Three PGD attempts were made, none of which resulted in a pregnancy [60].

In 2009, Shefi et al. reported a successful PGD in a 32-year-old woman with 22q11.2 deletion syndrome, with typical facial features and velopharyngeal anomaly. She has a 3-year-old daughter who was diagnosed with DiGeorge syndrome shortly after birth. FISH was used to detect 22q11.2 deletions in the embryos, and after three PGD attempts, the family gave birth to a healthy female baby [61].

References

1. Chun H, Gatti R. Ataxia-telangiectasia, an evolving phenotype. DNA Repair. 2004;3(8-9):1187–96.
2. Swift M et al. The incidence and gene frequency of ataxia-telangiectasia in the United States. Am J Hum Genet. 1986;39:573–83.
3. Biton S, Barzilai A, Shiloh Y. The neurological phenotype of ataxia-telangiectasia: solving a persistent puzzle. DNA Repair (Amst). 2008;7(7):1028–38.
4. Perlman S, Becker-Catania S, Gatti R. Ataxia telangiectasia: a diagnosis and treatment. Semin Pediatr Neurol. 2003;10(3):173–82.
5. Swift M et al. Malignant neoplasms in the families of patients with ataxia-telangiectasia. Cancer Res. 1976;36(1):209–15.
6. Morrell D, Chase C, Swift M. Cancers in 44 families with ataxia-telangiectasia. Cancer Genet Cytogenet. 1990;50:119–23.
7. Athma P, Rappaport R, Swift M. Molecular genotyping shows that ataxia-telangiectasia heterozygotes are predisposed to breast cancer. Cancer Genet Cytogenet. 1996;92:130–4.
8. Easton D. Cancer risks in A-T heterozygotes. Int J Radiat Biol. 1994;66:S177–82.
9. FitzGerald M et al. Heterozygous ATM mutations do not contribute to early onset breast cancer. Nat Genet. 1997;15:307–10.
10. Broeks A et al. ATM-heterozygous germline mutations contribute to breast cancer-susceptibility. Am J Hum Genet. 2000;66:494–500.
11. Renwick A et al. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nat Genet. 2006;38:873–5.

12. Jones K. Smith's recognizable patters of human malformation. 6th ed. Philadelpia: Elsevier Saunders; 2006.
13. Zadik Z et al. Gonadal dysfunction in patients with ataxia telangiectasia. Acta Paediatr Scand. 1978;67(4):477–9.
14. Crawford D, Acuna J, Sherman S. FMR1 and the fragile X syndrome: human genome epidemiology review. Genet Med. 2001;3:359–71.
15. Crawford D et al. Prevalence of the fragile X syndrome in African-Americans. Am J Med Genet. 2002;110:226–33.
16. Strom C et al. Molecular testing for Fragile X Syndrome: lessons learned from 119,232 tests performed in a clinical laboratory. Genet Med. 2007;9:46–51.
17. Sullivan S, Welt C, Sherman S. FMR1 and the continuum of primary ovarian insufficiency. Semin Reprod Med. 2011;29:299–307.
18. Monaghan KG et al. ACMG Standards and Guidelines for fragile X testing: a revision to the disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics and Genomics. Genet Med. 2013;15(7):575–86.
19. Nolin S et al. Expansion of the fragile X CGG repeat in females with premutation or intermediate alleles. Am J Hum Genet. 2003;72(2):454–64.
20. Fernandez-Carvajal I et al. Expansion of an FMR1 grey-zone allele to a full mutation in two generations. J Mol Diagn. 2009;11(4):306–10.
21. Yrigollen C et al. AGG interruptions within the maternal FMR1 gene reduce the risk of offspring with fragile X syndrome. Genet Med. 2012;14(8):729–36.
22. American College of Obstetrics and Gynecologists. Carrier screening for fragile X syndrome. Committee opinion No. 469. Obstet Gynecol. 2010;116:1008–10.
23. Pastore L, Morris W, Karns L. Emotional reaction to fragile X premuation carrier tests among infertile women. J Genet Couns. 2008;17(1):84–91.
24. Hagerman P, Hagerman R. The fragile-X premutation: a maturing perspective. Am J Hum Genet. 2004;74(5):805–16.
25. Sullivan A et al. Association of FMR1 repeat size with ovarian dysfunction. Hum Reprod. 2005;20(2):402–12.
26. Ennis S, Ward D, Murray A. Nonlinear association between CGG repeat number and age of menopause in FMR1 premutation carriers. Eur J Hum Genet. 2006;14:153–5.
27. De Caro J, Dominguez C, Sherman S. Reproductive health of adolescent girls who carry the FMR1 premutation: expected phenotype based on current knowledge of fragile X-associated primary ovarian insufficiency. Ann N Y Acad Sci. 2008;1135:99–111.
28. Nelson LM, Covington SN, Rebar RW. An update: spontaneous premature ovarian failure is not an early menopause. Fertil Steril. 2005;83(5):1327–32.
29. Sherman S, Pletcher B, Driscoll D. Fragile X syndrome: diagnostic and carrier testing. Genet Med. 2005;7(8):584–7.
30. Coss K et al. Classical Galactosaemia in Ireland: incidence, complications and outcomes of treatment. J Inherit Metab Dis. 2012;36:21–7.
31. Berry G, Elsas L. Introduction to the Maastricht workshop: lessons from the past and new directions in galactosemia. J Inherit Metab Dis. 2011;34:249–55.
32. van Erven B et al. Fertility preservation in female classic galactosemia patients. Orphanet J Rare Dis. 2013;8:107.
33. Fridovich-Keil J et al. Ovarian function in girls and women with GALT-deficiency galactosemia. J Inherit Metab Dis. 2011;34:357–66.
34. Levy H. Reproductive effects of maternal metabolic disorders: implications for pediatrics and obstetrics. Turk J Pediatr. 1996;38:335–44.
35. Levy H et al. Ovarian failure in galactosemia. N Engl J Med. 1984;310:50.
36. Rubio-Gozalbo M et al. Gonadal function in male and female patients with classic galactosemia. Hum Reprod Update. 2010;16:177–88.
37. Morrow R et al. Ovarian failure in a young woman with galactosaemia. Ulster Med J. 1985;54:218–20.

38. Robinson A et al. Hypergonadotrophic hypogonadism in classical galactosemia: evidence for defective oogenesis Case report. Br J Obstet Gynaecol. 1984;91:199–200.
39. Sauer M et al. Pregnancy after oocyte donation to a woman with ovarian failure and classical galactosemia. Fertil Steril. 1991;55:1197–9.
40. Gubbels C et al. Primary ovarian insufficiency in classic galactosemia: role of FSH dysfunction and timing of the lesion. J Inherit Metab Dis. 2013;36:29–34.
41. Gubbels C, Land J, Rubio-Gozalbo M. Fertility and impact of pregnancies on the mother and child in classic galactosemia. Obstet Gynecol Surv. 2008;63:334–43.
42. Tipton RE, Gorlin RJ. Growth retardation, alopecia, pseudo-anodontia, and optic atrophy--the GAPO syndrome: report of a patient and review of the literature. Am J Med Genet. 1984;19(2):209–16.
43. Stranecky V et al. Mutations in ANTXR1 cause GAPO syndrome. Am J Hum Genet. 2013;92(5):792–9.
44. Bayram Y et al. Whole exome sequencing identifies three novel mutations in ANTXR1 in families with GAPO syndrome. Am J Med Genet A. 2014;164A(9):2328–34.
45. Benetti-Pinto CL et al. GAPO syndrome: a new syndromic cause of premature ovarian insufficiency. Climacteric. 2016;19:1–5.
46. Cancrini C et al. Clinical features and follow-up in patients with 22q11.2 deletion syndrome. J Pediatr. 2014;164(6):1475–80. e2
47. Grassi MS et al. Congenital Heart Disease as a Warning Sign for the Diagnosis of the 22q11.2 Deletion. Arq Bras Cardiol. 2014;103(5):382–90.
48. Perez E, Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge and velocardiofacial syndromes). Curr Opin Pediatr. 2002;14(6):678–83.
49. Shaikh TH et al. Chromosome 22-specific low copy repeats and the 22q11.2 deletion syndrome: genomic organization and deletion endpoint analysis. Hum Mol Genet. 2000;9(4):489–501.
50. Yagi H et al. Role of TBX1 in human del22q11.2 syndrome. Lancet. 2003;362(9393):1366–73.
51. Driscoll DA. Prenatal diagnosis of the 22q11.2 deletion syndrome. Genet Med. 2001;3(1):14–8.
52. Noel AC et al. Fetal phenotype associated with the 22q11 deletion. Am J Med Genet A. 2014;164A(11):2724–31.
53. Peters D et al. Noninvasive prenatal diagnosis of a fetal microdeletion syndrome. N Engl J Med. 2011;365(19):1847–8.
54. Srinivasan A et al. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. Am J Hum Genet. 2013;92(2):167–76.
55. Lau TK et al. Secondary findings from non-invasive prenatal testing for common fetal aneuploidies by whole genome sequencing as a clinical service. Prenat Diagn. 2013;33(6):602–8.
56. Fernandez L et al. Comparative study of three diagnostic approaches (FISH, STRs and MLPA) in 30 patients with 22q11.2 deletion syndrome. Clin Genet. 2005;68(4):373–8.
57. Morcel K et al. Utero-vaginal aplasia (Mayer-Rokitansky-Kuster-Hauser syndrome) associated with deletions in known DiGeorge or DiGeorge-like loci. Orphanet J Rare Dis. 2011;6:9.
58. Markert ML et al. Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: outcome of 44 consecutive transplants. Blood. 2007;109(10):4539–47.
59. McDonald-McGinn DM, Zackai EH. Genetic counseling for the 22q11.2 deletion. Dev Disabil Res Rev. 2008;14(1):69–74.
60. Iwarsson E et al. Preimplantation genetic diagnosis of DiGeorge syndrome. Mol Hum Reprod. 1998;4(9):871–5.
61. Shefi S et al. Fish based preimplantation genetic diagnosis to prevent DiGeorge syndrome. J Assist Reprod Genet. 2009;26(7):411–3.

Chapter 7
Inborn Errors of Metabolism

Inborn errors of metabolism (IEMs) are a group of genetic disorders characterized by biochemical function abnormalities. Affected individuals in the United States are typically diagnosed by state-run newborn screening programs through their respective Departments of Public Health. Early diagnosis leads to early initiation of treatment and a significant decrease in morbidity and mortality. Infants and toddlers with inborn errors of metabolism may be candidates for hematopoietic stem cell transplantation (HSCT), which when conditioned with total body irradiation and gonadotoxic medications often results in infertility [1]. Fertility preservation options should be discussed with families prior to initiation of HSCT with special consideration of the hereditary nature of each condition and the possible disease-related impaired cognitive outcome.

Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplantation (HSCT) is a therapeutic option for some individuals with inborn errors of metabolism with deficiency of a primary enzyme. Given the rarity of each individual inborn error of metabolism, HSCT use is based on limited safety and efficacy data in humans. A detailed discussion with a biochemical geneticist is recommended to determine which patients may be eligible for HSCT. If HSCT is considered, the benefits must be weighed against the risk of procedure-related morbidity and mortality. A well-established risk of HSCT conditioned with total body irradiation (TBI) and high dose of gonadotoxic medications is infertility [1].

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_7

Female Fertility After Hematopoietic Stem Cell Transplant

HSCT conditioning with TBI and/or gonadotoxic drugs is associated with a high risk of ovarian failure in females [1, 2]. The majority (~90%) of females who are treated with TBI experience gonadal failure. Approximately 10% of females treated with TBI experience recovery of gonadal function, and only 1.3% achieve pregnancy [1].

Vatanen et al. (2013) evaluated long-term ovarian function after allogenic HSCT in childhood and adolescence in 70 prepubertal female transplant survivors and 22 adult transplant survivors (transplant occurring between 1987 and 2000; mean age of 9 years; age range 1–19 years). Results showed that 40/70 prepubertal females experienced spontaneous puberty, based on breast development, and 30/70 experienced spontaneous menarche. They found that there was a high risk of ovarian failure with conditioning TBI or Bu-based regimes prior to HSCT and intensive antileukemia therapy prior to HSCT, including CRT, decreased the possibility of spontaneous menarche [2].

Male Fertility After Hematopoietic Stem Cell Transplant

TBI and gonadotoxic drugs are typically used to condition patients prior to HSCT, both of which lead to the absence of spermatozoa. In fact, TBI is the main cause of azoospermia in patients treated with HSCT. This is due to the fact that spermatogenic stem cells are more sensitive to chemotherapy and radiation than later stage germ cells, preventing the generation of new sperm cells [1].

Rovo et al. (2013) conducted a European Group for Blood and Marrow Transplantation (EBMT) large retrospective analysis of men who underwent HSCT and found that 81% of males receiving TBI presented with azoospermia, and only 1% had normal sperm counts in follow-up sperm analysis [3].

Anserini et al. (2002) found that azoospermia is less frequent in patients conditioned with busulfan and cyclophosphamide (50%) and uncommon in those treated with cyclophosphamide alone. Suggesting, perhaps, that busulfan and cyclophosphamiade or cyclophosphamide alone may affect fertility less than traditional HSCT conditioning with TBI and gonadotoxic drugs [4].

Fertility Preservation Considerations

HSCT for inborn errors of metabolism is typically initiated in infancy or early childhood. Prepubertal females are unable to undergo the necessary ovarian stimulation needed for embryo and oocyte cryopreservation, and prepubertal males are unable

to produce a semen sample for semen cryopreservation. Therefore, at this time, experimental fertility preservation options including ovarian and testicular tissue cryopreservation are the only possible methods of fertility preservation for this population [5]. In 2014, Ginsberg et al. consented 57 families to testicular biopsy for the purposes of fertility preservation. From those 57 families, 28 children underwent testicular biopsy. Parents participating in the Ginsberg study reported that they made an informed decision and carefully weighed the risks and benefits of testicular tissue cryopreservation.

Individuals with inborn errors of metabolism undergoing HSCT may also consider adoption, donor sperm, donor eggs, or donor embryos when family planning if their fertility has been compromised.

Inborn Errors of Metabolism

Please note that this is not a complete list of known inborn errors of metabolism, rather it summarized those diseases known to have potentially reduced morbidity and mortality following HSCT.

Adrenoleukodystrophy

Prevalence

The prevalence of X-linked adrenoleukodystrophy (X-ALD) is 1 in 20,000–50,000 individuals worldwide. This condition occurs with a similar frequency in all populations [6].

Natural History

X-ALD is an X-linked recessive-inherited condition that primarily affects males (females are carriers). It is caused by pathogenic variants in *ABCD1*. *ABCD1* is a gene located on the X chromosome, which codes for adrenoleukodystrophy protein (ALDP). ALDP is an integral peroxisomal membrane protein that transports VLCFacyl-CoA esters from the cytosol to the peroxisome [6, 7]. Pathogenic variants in *ABCD1* lead to abnormal accumulation of saturated unbranched very long-chain fatty acids (VLCFAs) [8]. This accumulation is toxic in all tissues and causes oxidative stress and oxidative damage to proteins, microglial activation, and apoptosis [6]. The accumulation is greatest in the nervous tissue white matter, adrenal cortex, testis, and in some lipid fractions (e.g., cholesterol esters of the adrenal gland and brain) [8].

Disease Presentation

There are several subtypes of X-ALD with varying clinical features.

Cerebral Adrenoleukodystrophy

Approximately 50% of patients with X-ALD will develop the cerebral form of X-ALD at some point during their lifetime. The disease most frequently presents in childhood, typically between age 4 and 8 years, with the first noticeable symptom being a decline in school performance. The early clinical features of cerebral ALD are often misdiagnosed as attention deficit hyperactivity disorder (ADHD). Onset of the disease involves deficits in cognitive ability, including:

- Auditory discrimination or visual processing deficits
- Impaired spatial coordination
- Poor handwriting
- Impaired memory
- Poor attention and reasoning

Cerebral ALD progresses rapidly, and the neurological deficits quickly become more apparent. They include:

- Withdrawn or hyperactive behavior
- Apraxia
- Astereognosia
- Auditory impairment ("word deafness" reflecting impairment in acoustic analysis of word sounds)
- Decreased visual acuity
- Hemiparesis or spastic tetraparesis
- Cerebellar ataxia and seizures
- Primary adrenocortical insufficiency

Within 2–3 years, individuals with cerebral ALD typically have severe neurological disabilities that cause them to become bedridden, blind, and unable to speak or respond and require full-time nursing care and feeding by nasogastric tube or gastrostomy. Death typically follows [6, 7, 9].

Adrenomyeloneuropathy (AMN)

Virtually all patients with X-ALD who reach adulthood develop AMN, usually in the third or fourth decade of life. Their symptoms are limited to the spinal cord and peripheral nerves and include:

- Gradually progressive spastic paraparesis
- Sensory ataxia with impaired vibration sense

- Sphincter dysfunction (mostly urinary)
- Pain in legs
- Impotence
- Adrenocortical insufficiency (>70%) [6, 7, 9].

"Addison-Only" Presentation

Approximately 20% of male X-ALD patients have an "Addison-only" presentation, which presents as adrenocortical insufficiency without clinical or MRI evidence of neurological involvement. This may be the presenting symptom in boys and men years or even decades before the onset of neurological symptoms [6, 7, 9].

Asymptomatic and Presymptomatic Individuals

Individuals who are asymptomatic or presymptomatic are typically under age 7 years. They have normal cognitive function and are the key group for therapeutic interventions. Those who are presymptomatic are almost all at risk to develop neurologic (cerebral ALD or AMN) or endocrinologic (Addison's disease) symptoms [6].

Female Carriers

X-ALD is an X-linked recessive disorder. Females with one *ABCD1* pathogenic variant are carriers of the condition. Greater than 50% of female carriers exhibit some kind of abnormality on neurologic examination, most likely due to skewed X-inactivation in neuronal cells. Neurologic symptoms in carrier females have a typical onset between the fourth and fifth decade of life. Symptoms in female carriers are similar to those observed in males with AMN and include:

- Sensory ataxia
- Fecal incontinence
- Pain in the legs [6, 9]

Effect on Fertility

Management of X-ALD involves hematopoietic stem cell transplantation (HSCT). In 1990, HSCT led to stabilization and possibly reversal of neurological changes in a boy with early childhood cerebral X-ALD. The mechanisms of benefit have not yet been identified as donor cells do not enter the central nervous system (CNS). However, gradual replacement of a portion of perivascular microglia by

donor-derived cells may exert favorable metabolic effect, or the favorable effect may be due to the immunosuppression and reconstitution of the immune system by donor-derived cells. Regardless, HSCT is strongly recommended for patients at early stages of cerebral X-ALD but not for those in more advanced stages. The 5-year survival rate for those in early stages of illness is 92% [9].

Additional Considerations

Given that X-ALD is an inherited disorder, affected individuals and carriers may wish to discuss preimplantation genetic diagnosis (PGD) and/or prenatal testing (chorionic villus sampling or amniocentesis) with a reproductive geneticist or genetic counselor.

Alpha-Mannosidosis

Prevalence

The prevalence of alpha-mannosidosis is not precisely known. It is estimated that alpha-mannosidosis occurs in approximately one in 500,000 [10] to one in 1,000,000 live births and is expected to be found in every ethnic group [11].

Natural History

Alpha-mannosidosis is a rare lysosomal storage disorder that is inherited in an autosomal recessive manner due to pathogenic variants in *MAN2B1*. *MAN2B1* encodes alpha-mannosidase, a lysosomal enzyme responsible for the degradation of N-linked oligosaccharides. More specifically, alpha-mannosidase breaks down a sugar molecule called mannose. Individuals with alpha-mannosidosis have a deficiency of alpha-mannosidase leading to immune deficiency, facial and skeletal abnormalities, hearing impairment, and mental retardation [12].

Disease Presentation

Alpha-mannosidosis is a progressive disorder that can vary in severity. Individuals with the most severe form of the condition experience hepatomegaly and early childhood death due to recurrent severe infections. In contrast, those with the

attenuated form have a slow disease progression into adulthood with hearing loss and intellectual impairment.

The EU consortium HUE-MAN (working toward the development of an effective enzyme replacement therapy for human alpha-mannosidosis) conducted a longitudinal study on alpha-mannosidosis and thoroughly assessed the disease presentation [13]. Characteristics of the disease include:

- Mild to moderate intellectual disability (average IQ range 60–80)
- Delay of developmental milestones, specifically motor skill delay
- Late initiation of speech with restricted vocabulary
- Coarse facial features (prominent forehead, rounded eyebrows, flattened nasal bridge, prognathism, widely spaced teeth)
- Classically large head
- Unusually short neck
- Macroglossia
- Skeletal abnormalities (vertebral deformations and bowing of the legs)
- Osteopenia
- Deterioration of the bones and joints
- Psychiatric symptoms (>25%) [14]
  - Acute and recurrent attacks of confusion
  - Anxiety
  - Depression
  - Hallucinations
- Loss of function with decreased appetite, weight loss, and incontinence
- Ataxia
- Myopathy
- Hepatosplenomegaly
- Hydrocephalus [15]
- Hearing loss
- Cataracts
- Increased risk of infections

Effect on Fertility

Hematopoietic stem cell transplantation (HSCT) is the standard therapeutic option and currently the only clinically available treatment option, for alpha-mannosidosis [16]. Given the rarity of alpha-mannosidosis, HSCT use is based on limited safety and efficacy data in humans. The largest experience with HSCT for lysosomal storage diseases exists in Hurler syndrome, for which good long-term neurodevelopmental outcomes have been demonstrated.

Wall et al. (1998) presented a child with alpha-mannosidosis who underwent bone marrow transplant (BMT) and experienced complete resolution of recurrent

infectious disease and organomegaly, improvement in bone disease, and stabilization of neurocognitive function during a 2-year observational period [17]. Grewal et al. (2004) presented four patients, aged 3–23 years, who underwent HSCT and experienced intellectual function stabilization, hearing improvement to normal or near normal for speech frequencies (three-fourths of patients), no development of new skeletal abnormalities, and normalization of leukocyte enzyme activity. HSCT, therefore, is capable of halting the progressive cognitive loss in patients with alpha-mannosidosis when early diagnosis occurs [18]. Mynarek et al. (2012) conducted a retrospective multi-institutional analysis of 17 patients diagnosed with alpha-mannosidosis at a median age of 2.5 (1.1–23) years who underwent HSCT at a median age of 3.6 (1.3–23.1) years. At a median follow-up of 5.5 years, 88%, or 15 patients, were alive. The other two died within 5 months of HSCT. After HSCT, patients made developmental progress and the most improved is hearing. One patient, now an adult, has been reported to live an independent life. The retrospective study found that HSCT may be a feasible therapeutic option to promote mental development in individuals with alpha-mannosidosis [19].

Anytime HSCT use is considered, the benefits must be weighed against the overall risk of procedure-related morbidity and mortality. Additionally, benefits are greater in younger patients, prior to the development of disease complications. Therefore, HSCT is an option for children with alpha-mannosidosis during the first decade of life [20]. A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1].

Aspartylglucosaminidase

Prevalence

Aspartylglucosaminuria (AGU) affects individuals worldwide but is more prevalent among individuals of Finnish ancestry [21]. AGU affects approximately one in 3643 children in Finland, and approximately one out of every 30 Finnish individuals is a carrier of the autosomal recessive genetic condition [22].

Natural History

AGU is a rare, inherited lysosomal disease caused by pathogenic variants in *AGA*. *AGA* encodes the enzyme aspartylglucosaminidase (AGA). AGA enzyme is active within the lysosomes, where it helps break down complexes of sugar molecules (oligosaccharides) attached to glycoproteins. Pathogenic mutations in *AGA* cause an absence or shortage of AGA enzyme in the lysosomes, preventing the breakdown of oligosaccharides resulting in a buildup of glycoproteins that disrupt normal cell function, often resulting in cell destruction. Nerve cell destruction in the brain

causes many of the signs and symptoms of AGU, including progressive intellectual disability [23].

Disease Presentation

Infants with AGU appear healthy at birth and typically have normal development throughout early childhood. The first sign of the disease is usually delayed speech, which appears between ages 2 and 3 years. As the children age, a mild intellectual disability becomes apparent, and learning occurs at a slower than normal pace. Children with AGU are prone to upper respiratory infections and are tall for their age. They have a characteristic facial appearance with ocular hypertelorism, small ears, full lips, short and broad nose, a square-shaped face, and overgrown oral mucosa and facial skin.

In adolescence, the intellectual disability usually worsens. A maximal intellectual level and adaptive skills of a 5–6-year-old child is reached between 13 and 16 years of age before a decline of mental abilities occurs. Puberty typically occurs early in individuals with AGU—girls experience menarche at an average age of 10 years and young boys typically have macroorchidism. Adolescents with AGU do not experience a growth spurt during puberty and therefore tend to have short stature.

Adults with AGU have profound mental retardation with a limited vocabulary. They tend to be quiet and calm; however when disturbed, they can be aggressive. Approximately 25% of adults with AGU experience behavioral disturbances. After age 25–28 years, rapid mental and physical retardation occurs with death on average in mid-adulthood [21, 24, 25].

Effect on Fertility

Hematopoietic stem cell transplantation (HSCT) can provide the deficient enzyme AGA to individuals with AGU. The outcome of HSCT depends on how rapid the natural disease progression occurs, at what age the HSCT is performed, and the influence of transplant-related complications; therefore, HSCT should not be encouraged for the treatment of patients with AGU after infancy to increase the likelihood of a successful outcome [26].

Malm et al. (2004) conducted a 5-year follow-up after two siblings with AGU underwent HSCT using unrelated human leukocyte antigen A and B and DR identical donors at age 10 years 5 months and 5 years 10 months, respectively. After 5 years, no neuropsychological or clinical deterioration was noted in either sibling. Additionally, both siblings had stable expression of AGA [25]. Therefore, HSCT may arrest disease progression and could contribute to a better quality of life in individuals with AGU. Additional research is needed.

Arvio et al. (2001) described 19 young patients with AGU. Of the 19 individuals, five had undergone successful bone marrow transplantation between 1991 and 1997. Two patients who received transplants were more severely mentally retarded at seven and 5 years' follow-up than the non-transplanted patients. Additionally, all five individuals experienced posttransplant complications. Therefore, Arvio et al. (2001) concluded that bone marrow transplantation should not be recommended to patients after infancy [26].

AGU is a rare condition, and therefore HSCT use is based on limited safety and efficacy data in humans. The largest experience with HSCT for lysosomal storage diseases exists in Hurler syndrome, for which good long-term neurodevelopmental outcomes have been demonstrated. Therefore, it is possible that early HSCT during infancy may be beneficial in alleviating the disease symptoms and progression of AGU, including neurologic function [26]. Overall, the goal of HSCT is to cure the patient from the primary disease and restore complete physical and mental health condition; however, infertility is common after myeloablative HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs [1].

Fucosidosis

Prevalence

Fucosidosis is a rare condition. The prevalence is unknown.

Natural History

Fucosidosis is an inherited autosomal recessive disorder. It is caused by mutations in the *FUCA1* gene. *FUCA1* provides instructions to create alpha-L-fucosidase, an enzyme that breaks down complex sugar molecules in the body. Its job is to cleave off fucose, a sugar molecule, from proteins and fats to help the body use energy. When an individual has two non-working copies of *FUCA1*, they do not produce enough alpha-L-fucosidase enzyme to breakdown glycolipids and glycoproteins in the body. This causes the compounds to build-up within the body, including in the brain, which leads to cell death. Loss of brain cells is thought to cause the neurological disease and deficits among individuals with fucosidosis [27, 28].

Disease Presentation

Fucosidosis is a variable condition. It is a severe disease that typically presents in infancy with a life expectancy of late childhood. Less severe fucosidosis may present at age 1 or 2 years with a life expectancy of mid-adulthood. Clinical features vary among individuals, they include [27]:

- Variable intellectual disability
- Progressive spastic quadriplegia
- Coarse facies
- Growth retardation
- Visceromegaly
- Angiokeratoma corporis diffusum
- Recurrent bronchopneumonias
- Seizures
- Dysostosis multiplex

Effect on Fertility

Canine models of HSCT for treatment of fucosidosis show that neonatal transplantation prevents neurological disease [29]. HSCT may be an experimental treatment option for human infants with fucosidosis. A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their infant with fucosidosis may wish to consider fertility preservation in the event of long-term survival without neurological deterioration.

Gaucher Disease

Prevalence

Gaucher disease affects 1 in 50,000 to 1 in 100,000 individuals. Type I Gaucher disease is the most common and occurs more frequently among individuals of Ashkenazi Jewish ancestry. Approximately 1 in 15 Ashkenazi Jewish individuals is a carrier of type I Gaucher disease [30].

Natural History

Gaucher disease is an inherited autosomal recessive disorder. It is caused by mutations in the *GBA* gene. *GBA* provides instructions to create beta-glucocerebrosidase, a lysosomal enzyme acid. Beta-glucocerebrosidase breaks down glucocerebroside into sugar and a fat molecule during metabolism [31]. When an individual has two non-working copies of *GBA*, they do not produce enough of this enzyme, which allows glucocerebroside to accumulate within the body. Accumulation of glucocerebroside is toxic and damages the organs, causing the features of Gaucher disease.

Disease Presentation

Type I Gaucher Disease

Type I Gaucher disease is variable and can present anytime from childhood to adulthood. It is characterized by hepatosplenomegaly, anemia, thrombocytopenia, lung disease, and bone disease. It typically does not involve the central nervous system.

Types II and III Gaucher Disease

Types II and III Gaucher disease affect the central nervous system and can cause brain damage, seizures, and vision abnormalities. Complications of type II Gaucher disease are usually life-threatening in infancy.

Additional forms of Gaucher disease exist, such as the perinatal lethal form and cardiovascular type [32].

Effect on Fertility

While type I Gaucher disease is effectively treated by enzyme therapy, there are no approved therapies for individuals with type II (infantile) and type III (Norbottnian–Swedish) Gaucher disease [33]. These individuals may be eligible for HSCT [34, 35]. If engraftment is successful, there may be reduction of CNS signs and symptoms. A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their infant with types II or III Gaucher disease may wish to consider fertility preservation in the event of long-term survival.

Hunter Syndrome

Prevalence

Hunter syndrome, a mucopolysaccharidosis type II (MPS II) condition, occurs in approximately 1 in 170,000 males [36].

Natural History

Hunter syndrome is an inherited X-linked recessive disorder. It is caused by mutations in the *IDS* gene, which is located on the X chromosome. *IDS* provides instructions to make the I2S enzyme, which helps breakdown large sugar molecules in the

body called glycosaminoglycans (GAGs). Males with a mutation in their *IDS* gene have reduced or absent I2S activity which leads to an accumulation of GAGs inside the cells' lysosomes leading to disease [37].

Disease Presentation

Hunter syndrome is a variable disease with multiorgan and multisystem involvement. Severely affected individuals may present within the first 2–4 years of life and have an average life span of one to two decades.

Features of Hunter syndrome include:

- Coarse features
- Deep, hoarse voice
- Airway obstruction
- Sleep apnea
- Macrocephaly
- Hydrocephalus
- Hepatosplenomegaly
- Umbilical and inguinal hernias
- Hearing loss
- Reduced vision
- Retinal abnormalities
- Spinal stenosis
- Heart valve abnormalities
- Ventricular hypertrophy
- Short stature
- Joint contractures
- Dysostosis multiplex
- Intellectual disability

Less common, mildly affected individuals may not develop symptoms until later in life, demonstrate normal intelligence, and survive into adulthood [37].

Effect on Fertility

HSCT has been proposed for individuals with Hunter syndrome to slow or stop disease progression. Early case reports of HSCT for Hunter syndrome were generally unsuccessful [38–41]. However, among 12 individuals with Hunter disease who received HSCT, all 12 were still living after 3 years. Those between 2 and 6 years of age at transplant demonstrated improvements in motor and speech skills, suggesting HSCT may be beneficial in improving mental development among young boys with Hunter syndrome [42]. Additional research and long-term follow-up are needed to determine the effects of transplantation on neurological development.

A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their young son with Hunter disease may wish to consider fertility preservation in the event of long-term survival.

Hurler Syndrome

Prevalence

Hurler syndrome, a mucopolysaccharidosis type 1 (MPS I) condition, occurs in approximately 1 in 100,000 infants born [43]. It is a panethnic condition, affecting individuals all over the world; however, there is a higher proportion of infants born with Hurler syndrome in North America and Europe than in Latin America or the Asia Pacific region. This may be due to differences in genetic landscape or the result of regional differences in diagnosis and enrollment of Hurler syndrome patients into the voluntary MPS I registry. The MPS I registry includes 987 MPS I patients worldwide, 60.9% of which have the most severe MPS I disorder, Hurler syndrome [13].

Natural History

MPS I is a rare autosomal recessive-inherited disease caused by a deficiency of alpha-L-iduronidase, an enzyme required for the degradation of the glycosaminoglycans (GAGs) dermatan and heparin sulfate. It is caused by pathogenic mutations in the *IDUA* gene. The chronic and progressive accumulation of GAGs in the lysosomes of cells throughout the body leads to multiorgan dysfunction and considerable morbidity. If untreated, patients with Hurler syndrome typically experience progressive deterioration of the musculoskeletal, cardiorespiratory, and central nervous systems. Death typically occurs before age 10 years [43].

Disease Presentation

MPS I varies significantly with regard to disease presentation and course of disease. This may be due to differences among affected individuals in the severity of the underlying *IDUA* pathogenic variants and consequent residual degree of enzyme activity [44]. Delineation of the different MPS I phenotypes can be challenging [45]; the three MPS I subtypes are:

- *Scheie syndrome*: a mild MPS I phenotype with late onset of typically mild symptoms and slower disease progression. Individuals with Scheie syndrome are

expected to have normal intelligence and survive into adulthood; however, Scheie syndrome does have significant disease morbidity.
- *Hurler–Scheie syndrome*: an intermediate phenotype with mild to no cognitive impairment and reduced life expectancy. Death often occurs in the second or third decade.
- *Hurler syndrome*: the most severe form of MPS I. Hurler syndrome symptoms emerge shortly after birth and progress rapidly. Most individuals with Hurler syndrome die within the first decade of life. Hurler syndrome symptoms include developmental delay and cognitive decline, characteristic coarse facial features, joint stiffness and contractures, short stature, and respiratory, cardiac, and hepatic disease [45].

The MPS I registry reports the following findings in individuals with Hurler syndrome [13]:

- Coarse facial features (86.4%)
- Corneal clouding (70.9%)
- Hepatomegaly (70.0%)
- Kyphosis/gibbus (70.0%)
- Hernias (58.9%)
- Airway-related symptoms, such as sleep disturbances/snoring (51.6%)
- Splenomegaly (50.9%)
- Cardiac valve abnormalities (48.9%)
- Cognitive impairment (46.4%)
- Dysostosis multiplex (43.6%)
- Enlarged tongue (41.3%)
- Joint contractures (37.9%)
- Enlarged tonsils (28.6%)

Effect on Fertility

Since 1980, hematopoietic stem cell transplantation (HSCT) has been used to treat Hurler syndrome. Wang et al. (2016) reported an overall survival at 3 years of 82.5% for 12 individuals with MPS 1 [42]. Hurler–Scheie and Scheie syndromes are not traditionally treated with HSCT. Instead, individuals with Hurler–Scheie and Scheie syndromes receive enzyme replacement therapy (ERT) with laronidase (recombinant alpha-L-iduronidase, Aldurazyme) as the primary treatment [13].

HSCT is recommended for patients with Hurler syndrome under the age of 2 years with normal cognitive function (defined as IQ >70) [46]. When successful, it is a one-time procedure that can prolong survival, preserve cognitive function, and reduce morbidity [47]. HSCT reduces Hurler syndrome disease morbidity with substantial clinical benefit, including alleviation of hepatosplenomegaly, upper airway obstruction (including sleep apnea), cardiac symptoms, and coarse facial features. Unfortunately, early diagnosis of Hurler syndrome is limited by several factors,

including rarity of the disease, wide variability in clinical presentation and disease course, and the nonspecific nature of early disease manifestations [46].

The goal of HSCT is to cure the patient from the primary disease and restore complete physical and mental health condition; however, infertility is common after myeloablative HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs [1].

Krabbe Disease

Prevalence

Krabbe disease, also called globoid cell leukodystrophy, affects approximately 1 in every 100,000 individuals. It is estimated that 1 in 150 individuals is a carrier of Krabbe disease; however, there are subsets of the population in Israel where the carrier rate is approximately one in six [48].

Natural History

Krabbe disease is an inherited autosomal recessive disorder. It is caused by mutations in the *GALC* gene. *GALC* provides instructions to create the enzyme galactosylceramidase. Galactosylceramidase helps break down fats in the body. It is also an important part of myelin- the protective covering surrounding nerve cells. When an individual has two non-working copies of *GALC,* they do not produce enough galactosylceramidase. A deficiency of galactosylceramidase leads to loss of myelin, which prevents the nerves in the body from functioning properly resulting in the disease [49–51].

Disease Presentation

Krabbe disease most commonly presents in infancy with irritability, difficulty feeding, poor head control, and low muscle tone. Untreated infants typically experience rapid progressive neurologic deterioration, which impacts their ability to see, hear, move, and eat. Typical life span without treatment is less than 2 years. Krabbe disease can also present in childhood with a similar progressive decline.

Krabbe disease that presents in adolescence, or adulthood, is quite variable. Common initial symptoms include problems with vision, muscle weakness, gait changes, and intellectual regression. Survival among those with onset in adolescence and adulthood is variable [50].

Effect on Fertility

Prompt diagnosis of Krabbe disease in affected children allows them to potentially benefit from HSCT, which is currently the only approved and available treatment for Krabbe disease [50, 51]. Transplanted stem cells provide the missing galactosylceramidase enzyme, which leads to remyelination of the nerves [52]. HSCT has been shown to reverse ongoing severe central nervous system deterioration in both early infantile and late-onset Krabbe disease [53, 54]. A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their child with Krabbe disease may wish to consider fertility preservation in the event of long-term survival.

Lysosomal Acid Lipase Deficiency

Prevalence

Lysosomal acid lipase (LAL) deficiency is rare and under-recognized. The most severe form, known as Wolman disease, is estimated to have a prevalence of 1 in 350,000. Milder phenotypes, such as cholesterol ester storage disease (CESD), may occur in more than 1 in 50,000 individuals [55].

Natural History

LAL deficiency is an inherited autosomal recessive disorder. It is caused by mutations in the *LIPA* gene. *LIPA* provides instructions to create lysosomal acid lipase, an enzyme that is active in the lysosomes of the cell. Lysosomal acid lipase breaks down lipids for use in the body. When an individual has two non-working copies of *LIPA*, they do not produce enough lysosomal acid lipase. This results in excess lipids, such as triglycerides and cholesterol esters, to accumulate in the body leading to the signs and symptoms of LAL deficiency [56, 57].

Disease Presentation

LAL deficiency is a variable condition. Severity has some relation to the amount of residual enzyme activity, but a clinical diagnosis of Wolman disease or CESD is typically dependent on age of symptom onset.

The most severe form of LAL deficiency, Wolman disease, is characterized by 5% or lower residual LAL activity [58]. Wolman disease presents in infancy. It may

present immediately with vomiting, steatorrhea, and abdominal distension, or it may present after a few weeks of life as failure to thrive [59, 60]. Additional features and complications of Wolman disease include:

- Hepatomegaly
- Splenomegaly
- Malnutrition
- Liver failure
- Adrenal cortical insufficiency

The average life span of an infant with Wolman syndrome is typically under 1 year due to complications of malnutrition, liver disease, and adrenal cortical insufficiency [61, 62]. However, successful hematopoietic stem cell transplantation (HSCT) may decrease morbidity and mortality by correcting the metabolic defect [63]. Enzyme replacement therapy (ERT) with sebelipase alfa, approved in 2015 by the FDA, is also an option for individuals with Wolman disease [64].

The more mild form of LAL deficiency, CESD, is characterized by 2–11% of residual LAL activity [58]. CESD may present in childhood as failure to thrive and developmental delay [65], or it may present later in life as hepatosplenomegaly with or without elevated liver enzymes and/or serum lipid abnormalities [66]. Signs and symptoms of CESD include:

- Atherosclerosis
- Liver disease
- Organomegaly
- Malabsorption

Morbidity is variable among individuals with CESD. Affected individuals are recommended to consume a diet low in cholesterol and triglycerides. Statins may also be helpful. ERT with sebelipase alfa has been shown to prolong survival for those with CESD [64]. Additionally, affected individuals may wish to consider HSCT to attempt to correct the metabolic defect.

Effect on Fertility

Without HSCT or ERT, infants with Wolman disease are typically not expected to survive their first year of life. HSCT is considered a treatment for Wolman disease because the donor cells supply lysosomal enzyme acid lipase to the lysosomes of host cells, which restores sufficient enzyme activity for normal break down of lipids. Tolar et al. (2009) reported their results of HSCT for four individuals with Wolman syndrome, two of whom resulted in successful longer-term survival—4 and 11 years at the time of publication. Graft failure and high mortality rate associated with pretransplant liver injury and posttransplant veno-occlusive disease are barriers to optimal outcome of HSCT among individuals with Wolman disease [67,

68]. Gramatges et al. (2009) reported evidence of Wolman disease in their patient following HSCT despite normal lysosomal acid lipase activity; therefore, the degree of underlying hepatic pathological damage observed in pre-HSCT may be predictive of clinical outcome.

A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their infant with Wolman disease may wish to consider fertility preservation in the event of long-term survival.

FDA approval of sebelipase alfa ERT presents an alternative or subsequent treatment for Wolman disease [64]. The use of sebelipase alfa could follow HSCT to secure a continuous amount of normal enzyme to all tissues involved [54]. It is currently not known if there are any direct or indirect harmful effects with respect to fertility and fetal development as a result of the exposure of sebelipase alfa before or during pregnancy.

Adult females with CESD who undergo liver transplantation may wish to discuss their fertility options with their healthcare providers. While there is a good success rate of pregnancy in liver transplant recipients, the pregnancy itself poses a high risk to the woman, fetus, and liver [69]. Pregnancy post-liver transplant should involve close monitoring by subspecialists. Additionally, immunosuppressive agents used to treat pregnant women posttransplant may not be safe for use in pregnancy, including azathioprine and mycophenolate mofetil [70]. Women may wish to consider alternative family planning options such as surrogacy and adoption.

Maroteaux–Lamy Syndrome (MPS VI)

Prevalence

Maroteaux–Lamy syndrome, or mucopolysaccharidosis type VI, is a rare disorder. The prevalence is estimated to be 1 in 1,300,000 [71]. There may be a local founder effect in Northern Portugal and areas of Brazil [72].

Natural History

Maroteaux–Lamy syndrome is an inherited autosomal recessive disorder. It is caused by mutations in the *ARSB* gene. *ARSB* provides instructions to create arylsulfatase B, an enzyme involved in the breakdown of glycosaminoglycans (GAGs). When an individual has two non-working copies of *ARSB*, they do not produce enough arylsulfatase B, which allows GAGs to accumulate within the body, specifically within the lysosomes of cells. Accumulation of GAGs causes the features of Maroteaux–Lamy syndrome [73].

Disease Presentation

Maroteaux–Lamy syndrome has variable features and severity. Affected individuals typically begin to show signs and symptoms during early childhood. They may present with macrocephaly, coarse facial features, macroglossia, and hepatosplenomegaly. Additionally, affected individuals may have short stature, dysostosis multiplex, stiff joints, corneal clouding, and cardiac abnormalities. Intelligence is typically normal. Life expectancy is variable and dependent on the severity of symptoms; it can range from late childhood to adulthood [71, 73].

Effect on Fertility

Successful HSCT has been described for Maroteaux–Lamy syndrome. HSCT has the potential to provide physiologic levels of the deficiency in arylsulfatase B enzyme. It has been reported to have long-term outcomes of reduction of facial dysmorphism and improvement and stabilization of cardiac manifestations. HSCT has not been shown to improve skeletal abnormalities [54, 71, 74, 75].

A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their child with Maroteaux–Lamy syndrome may wish to consider fertility preservation in the event of long-term survival.

Morquio Syndrome (MPS IV)

Prevalence

Morquio syndrome, or mucopolysaccharidosis type IV, is a rare disorder. The prevalence is unknown.

Natural History

Morquio syndrome is an inherited autosomal recessive disorder. It is caused by mutations in the *GALNS* and *GLB1* genes. These genes provide instructions to produce enzymes involved in the breakdown of glycosaminoglycans (GAGs). When an individual has two non-working copies of either *GALNS* or *GLB1*, they do not produce enough enzyme, which allows GAGs to accumulate within the body, specifically within the lysosomes of cells. Accumulation of GAGs causes the features of Morquio syndrome [76–79].

Disease Presentation

Morquio syndrome is variable in severity. The main characteristics of Morquio syndrome include short stature, skeletal dysplasia, dental anomalies, and corneal clouding. Affected individuals are expected to have normal intelligence. The most severely affected individuals typically do not live past the second or third decade of life without treatment [79].

Effect on Fertility

HSCT may be a therapeutic option for individuals with Morquio syndrome. Yabe et al. (2016) conducted a long-term study of HSCT for the treatment of Morquio syndrome and found that it successfully demonstrated therapeutic effect with respect to halting respiratory disease progression and improving activities of daily living [80].

A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their child with Morquio syndrome may wish to consider fertility preservation in the event of long-term survival.

Mucolipidosis II

Prevalence

Mucolipidosis II, also called I-cell disease, is a rare disorder with an unknown prevalence.

Natural History

Mucolipidosis II is an inherited autosomal recessive disorder. It is caused by mutations in the *GNPTAB* gene. *GNPTAB* provides instructions to create part of the GlcNAc-1-phosphotransferase enzyme. This enzyme attaches mannose-6-phosphate (M6P) to specific digestive enzymes to assist with transport to the lysosomes. When an individual has two non-working copies of *GNPTAB*, they do not produce enough of this enzyme, which prevents transport of digestive enzymes to the lysosomes. Without digestive enzymes in the lysosomes, other large molecules accumulate. This accumulation in the lysosomes causes the features of mucolipidosis II [81, 82].

Disease Presentation

Mucolipidosis II is a progressive disorder in which affected individuals do not typically survive past early childhood. Characteristics include coarse facial features, short stature, skeletal abnormalities, cardiomegaly, and developmental delay [83].

Effect on Fertility

HSCT is an investigational therapy for mucolipidosis II. There are reports of individuals with mucolipidosis II experiencing continued neurocognitive development and prevention of cardiopulmonary complications following HSCT [54]. A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their child with mucolipidosis II may wish to consider fertility preservation in the event of long-term survival.

Sanfilippo Syndrome (MPS III)

Prevalence

Sanfilippo syndrome is the most common type of mucopolysaccharidosis. It is estimated to affect as many as 1 in every 58,000 newborns [84].

Natural History

Sanfilippo syndrome is an inherited autosomal recessive disorder. It is caused by mutations in the *GNS, HGSNAT, NAGLU,* and *SGSH* genes. These genes provide instructions to produce enzymes involved in the breakdown of glycosaminoglycans (GAGs). When an individual has two non-working copies of the same gene, they do not produce enough enzyme, which allows GAGs to accumulate within the body, specifically within the lysosomes of cells. Accumulation of GAGs causes the features of Sanfilippo syndrome [85].

Disease Presentation

Sanfilippo syndrome is a progressive neurological disorder. Signs and symptoms typically present in early childhood and may include delayed speech and behavior problems. Over time, affected individuals may experience progressive intellectual

disability, developmental regression, seizures, and movement abnormalities. Individuals may also have features typical of mucopolysaccharidosis, including coarse facial features, macrocephaly, hepatomegaly, and dysostosis multiplex [86, 87].

Effect on Fertility

The use of HSCT for Sanfilippo syndrome is controversial. Data has shown poor developmental outcome following HSCT. In the future, enzyme replacement therapy may be used in combination with HSCT. If HSCT is being performed as experimental treatment for Sanfilippo syndrome, discussions of fertility preservation may be of some interest to parents. A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]. However, given lack of positive outcomes from HSCT, fertility preservation may not be warranted for individuals with Sanfilippo syndrome at this time.

Sly Syndrome (MPS VII)

Prevalence

Sly syndrome, or mucopolysaccharidosis type VII, is one of the more rare types of mucopolysaccharidosis. Epidemiologic data is scarce [77].

Natural History

Sly syndrome is an inherited autosomal recessive disorder. It is caused by mutations in the *GUSB* gene. *GUSB* provides instructions to create the beta-glucuronidase enzyme. This enzyme helps break down glycosaminoglycans (GAGs). When an individual has two non-working copies of *GUSB*, they do not produce enough of this enzyme, which allows GAGs to accumulate within the body, specifically within the lysosomes of cells. Accumulation of GAGs causes the features of Sly syndrome [77].

Disease Presentation

Sly syndrome is extremely variable. The most severely affected individuals have hydrops fetalis, while those who are mildly affected develop symptoms later in life. Characteristics of Sly syndrome include intellectual disability, short stature,

hepatosplenomegaly, and bone dysplasia. Individuals who present later in life typically have normal intelligence [77, 88].

Effect on Fertility

When successful, HSCT is a one-time procedure that can prolong survival, preserve cognitive function, and reduce morbidity for individuals with mucopolysaccharidosis [47]. Due to the rarity of Sly syndrome, limited information exists regarding HSCT use as treatment. There are reports of individuals with Sly syndrome experiencing remission of signs and symptoms following HSCT [54]. A well-established risk of HSCT conditioned with total body irradiation (TBI) and high doses of gonadotoxic drugs is infertility [1]; therefore, families considering HSCT for their child with Sly syndrome may wish to consider fertility preservation in the event of long-term survival.

References

1. Tichelli A, Rovo A. Fertility issues following hematopoietic stem cell transplantation. Expert Rev Hematol. 2013;6(4):375–88.
2. Vatanen A et al. Ovarian function after allogenic hematopoietic stem cell transplantation in childhood and adolescence. Eur J Endocrinol. 2013;170(2):211–8.
3. Rovo A et al. Ongoing graft-versus-host disease is a risk factor for azoospermia after allogeneic hematopoietic stem cell transplantation. A survey of the late effect working party of the European Group for Blood and Marrow Transplantation. Haematologica. 2013;98(3):339–45.
4. Anserini P et al. Semen analysis following allogenic bone marrow transplantation. Additional data for evidence-based counselling. Bone Marrow Transplant. 2002;30(7):447–51.
5. Ginsberg J et al. Testicular tissue cryopreservation in prepubertal male children: An analysis of parental decision-making. Pediatr Blood Cancer. 2014;61(9):1673–8.
6. Engelen M et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. 2012;7:51.
7. Kemp S, Wanders R. Biochemical aspects of X-linked adrenoleukodystrophy. Brain Pathol. 2010;20(4):831–7.
8. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. Brain. 1997;120(Pt 8):1485–508.
9. Moser HW. Therapy of X-linked adrenoleukodystrophy. NeuroRx. 2006;3(2):246–53.
10. Meikle P et al. Newborn screening for lysosomal storage disorders: clinical evaluation of a two-tier strategy. Pediatrics. 2004;114:909–16.
11. Meikle P et al. Prevalence of lysosomal storage disorders. JAMA. 1999;281:249–54.
12. Beck M et al. Natural history of alpha mannosidosis a longitudinal study. Orphanet J Rare Dis. 2013;8:88.
13. Beck M et al. The natural history of MPS I: global perspectives from the MPS I Registry. Genet Med. 2014;16(10):759–65.
14. Malm D, Pantel J, Linaker O. Psychiatric symptoms in alpha-mannosidosis. J Intellect Disabil Res. 2005;49:865–71.

15. Halperin J et al. Communicating hydrocephalus and lysosomal inclusions in mannosidosis. Arch Neurol. 1984;41:777–9.
16. Prasad V, Kurtzberg J. Cord blood and bone marrow transplantation in inherited metabolic diseases: scientific basis, current status and future directions. Br J Haematol. 2010;148:356–72.
17. Wall D et al. Bone marrow transplantation for the treatment of alpha-mannosidosis. J Pediatr. 1998;133:282–5.
18. Grewal S et al. Effective treatment of alpha-mannosidosis by allogeneic hematopoietic stem cell transplantation. J Pediatr. 2004;144:569–73.
19. Mynarek M et al. Allogenic hematopoietic SCT for alpha-mannosidosis: an analysis of 17 patients. Bone Marrow Transplant. 2012;47(3):352–9.
20. Malm D, Nissen O. Alpha-mannosidosis. Orphanet J Rare Dis. 2008;3:21.
21. Arvio P, Arvio M. Progressive nature of aspartylglucosaminuria. Acta Paediatr. 2002;91(3):255–7.
22. Mononen I et al. Aspartylglucosaminuria in the Finnish population: identification of two point mutations in the heavy chain of glycoasparaginase. Proc Natl Acad Sci. 1991;88:2941–5.
23. Aronson NJ. Aspartylglucosaminuria: biochemistry and molecular biology. Biochim Biophys Acta. 1999;1455(2–3):139–54.
24. Arvio M et al. Dysmorphic facial features in aspartylglucosaminuria patients and carriers. Clin Dysmorphol. 2004;13(1):11–5.
25. Malm G et al. Five-year follow-up of two siblings with aspartylglucosaminuria undergoing allogeneic stem-cell transplantation from unrelated donors. Transplantation. 2004;78(3):415–9.
26. Arvio M, Sauna-aho O, Peippo M. Bone marrow transplantation for aspartylglucosaminuria: follow-up study of transplanted and non-transplanted patients. J Pediatr. 2001;138:288–90.
27. Ben Turkia H et al. Phenotypic spectrum of fucosidosis in Tunisia. J Inherit Metab Dis. 2008;31(Suppl 2):S313–6.
28. Cragg H et al. Fucosidosis: genetic and biochemical analysis of eight cases. J Med Genet. 1997;34(2):105–10.
29. Kondagari GS et al. Treatment of canine fucosidosis by intracisternal enzyme infusion. Exp Neurol. 2011;230(2):218–26.
30. Horowitz M et al. Prevalence of glucocerebrosidase mutations in the Israeli Ashkenazi Jewish population. Hum Mutat. 1998;12(4):240–4.
31. Beutler E. Gaucher disease, a paradigm for single gene defects. Experientia. 1995;51(3):196–7.
32. Rosenbloom BE, Weinreb NJ. Gaucher disease: a comprehensive review. Crit Rev Oncog. 2013;18(3):163–75.
33. Van Rossum A, Holsopple M. Enzyme replacement or substrate reduction? A review of Gaucher disease treatment options. Hosp Pharm. 2016;51(7):553–63.
34. Krivit W. Stem cell bone marrow transplantation in patients with metabolic storage diseases. Adv Pediatr. 2002;49:359–78.
35. Tang X et al. Treatment of Gaucher disease with allogeneic hematopoietic stem cell transplantation: report of three cases and review of literatures. Zhonghua Er Ke Za Zhi. 2015;53(11):810–6.
36. Baehner F et al. Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis. 2005;28(6):1011–7.
37. Martin R et al. Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). Pediatrics. 2008;121(2):e377–86.
38. Vellodi A et al. Long-term follow-up following bone marrow transplantation for Hunter disease. J Inherit Metab Dis. 1999;22(5):638–48.
39. Coppa GV et al. Bone marrow transplantation in Hunter syndrome (mucopolysaccharidosis type II): two-year follow-up of the first Italian patient and review of the literature. Pediatr Med Chir. 1995;17(3):227–35.

40. Mullen CA et al. Unrelated umbilical cord blood transplantation in infancy for mucopolysaccharidosis type IIB (Hunter syndrome) complicated by autoimmune hemolytic anemia. Bone Marrow Transplant. 2000;25(10):1093–7.
41. Peters C, Krivit W. Hematopoietic cell transplantation for mucopolysaccharidosis IIB (Hunter syndrome). Bone Marrow Transplant. 2000;25(10):1097–9.
42. Wang J et al. Allogeneic Hematopoietic Stem Cell Transplantation in Thirty-Four Pediatric Cases of Mucopolysaccharidosis-A Ten-Year Report from the China Children Transplant Group. Biol Blood Marrow Transplant. 2016;22(11):2104–8.
43. Neufeld E, Muenzer J. The mucopolysaccharidoses. In: Scriver C, Beaudet A, Sly W, editors. The metabolic and molecular bases of inherited disease. New York: McGraw Hill; 2001. p. 3421–52.
44. Terlato N, Cox G. Can mucopolysaccharidosis type I disease severity be predicted based on a patient's genotype? A comprehensive review of the literature. Genet Med. 2003;5:286–94.
45. Muenzer J, Wraith J, Clarke L, International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I. *Mucopolysaccharidosis I: management and treatment guidelines*. Pediatrics. 2009;123:19–29.
46. Peters C et al. Outcomes of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. Blood. 1996;87:4894–902.
47. Hobbs J et al. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone marrow transplantation. Lancet. 1981;318(8249):709–12.
48. Rafi MA et al. Two different mutations are responsible for Krabbe disease in the Druze and Moslem Arab populations in Israel. Hum Genet. 1996;97(3):304–8.
49. Bongarzone ER et al. Insights into the pathogenesis and treatment of Krabbe disease. Pediatr Endocrinol Rev. 2016;13(Suppl 1):689–96.
50. Escolar ML et al. Clinical management of Krabbe disease. J Neurosci Res. 2016;94(11):1118–25.
51. Karumuthil-Melethil S, Gray SJ. Immunological considerations for treating globoid cell leukodystrophy. J Neurosci Res. 2016;94(11):1349–58.
52. Siddiqi ZA, Sanders DB, Massey JM. Peripheral neuropathy in Krabbe disease: effect of hematopoietic stem cell transplantation. Neurology. 2006;67(2):268–72.
53. Krivit W et al. Hematopoietic stem-cell transplantation in globoid-cell leukodystrophy. N Engl J Med. 1998;338(16):1119–26.
54. Krivit W. Allogeneic stem cell transplantation for the treatment of lysosomal and peroxisomal metabolic diseases. Springer Semin Immunopathol. 2004;26(1–2):119–32.
55. Muntoni S et al. Prevalence of cholesteryl ester storage disease. Arterioscler Thromb Vasc Biol. 2007;27(8):1866–8.
56. Aslanidis C et al. Genetic and biochemical evidence that CESD and Wolman disease are distinguished by residual lysosomal acid lipase activity. Genomics. 1996;33(1):85–93.
57. Pagani F et al. New lysosomal acid lipase gene mutants explain the phenotype of Wolman disease and cholesteryl ester storage disease. J Lipid Res. 1998;39(7):1382–8.
58. Fasano T et al. Lysosomal lipase deficiency: molecular characterization of eleven patients with Wolman or cholesteryl ester storage disease. Mol Genet Metab. 2012;105(3):450–6.
59. Shome DK et al. The Middle-East connection of Wolman Disease. Saudi Med J. 2002;23(5):597–601.
60. Browne M et al. Wolman's disease in an infant. Br J Haematol. 2003;122(4):522.
61. Nchimi A, Rausin L, Khamis J. Ultrasound appearance of bowel wall in Wolman's disease. Pediatr Radiol. 2003;33(4):284–5.
62. Burton BK et al. Clinical Features of Lysosomal Acid Lipase Deficiency. J Pediatr Gastroenterol Nutr. 2015;61(6):619–25.
63. Gramatges MM et al. Pathological evidence of Wolman's disease following hematopoietic stem cell transplantation despite correction of lysosomal acid lipase activity. Bone Marrow Transplant. 2009;44(7):449–50.

64. Burton BK et al. A phase 3 trial of sebelipase alfa in lysosomal acid lipase deficiency. N Engl J Med. 2015;373(11):1010–20.
65. Bindu PS et al. Cholesterol ester storage disease with unusual neurological manifestations in two siblings: a report from South India. J Child Neurol. 2007;22(12):1401–4.
66. Drebber U et al. Severe chronic diarrhea and weight loss in cholesteryl ester storage disease: a case report. World J Gastroenterol. 2005;11(15):2364–6.
67. Tolar J et al. Long-term metabolic, endocrine, and neuropsychological outcome of hematopoietic cell transplantation for Wolman disease. Bone Marrow Transplant. 2009;43(1):21–7.
68. Yanir A et al. Unfavorable outcome of hematopoietic stem cell transplantation in two siblings with Wolman disease due to graft failure and hepatic complications. Mol Genet Metab. 2013;109(2):224–6.
69. Nagy S et al. Pregnancy outcome in liver transplant recipients. Obstet Gynecol. 2003;102(1):121–8.
70. Perales-Puchalt A et al. Pregnancy outcomes after kidney transplantation-immunosuppressive therapy comparison. J Matern Fetal Neonatal Med. 2012;25(8):1363–6.
71. Giugliani R, Harmatz P, Wraith JE. Management guidelines for mucopolysaccharidosis VI. Pediatrics. 2007;120(2):405–18.
72. Karageorgos L et al. Mutational analysis of mucopolysaccharidosis type VI patients undergoing a phase II trial of enzyme replacement therapy. Mol Genet Metab. 2007;90(2):164–70.
73. Azevedo AC et al. Clinical and biochemical study of 28 patients with mucopolysaccharidosis type VI. Clin Genet. 2004;66(3):208–13.
74. Herskhovitz E et al. Bone marrow transplantation for Maroteaux-Lamy syndrome (MPS VI): long-term follow-up. J Inherit Metab Dis. 1999;22(1):50–62.
75. Summers CG et al. Ocular changes in the mucopolysaccharidoses after bone marrow transplantation. A preliminary report. Ophthalmology. 1989;96(7):977–84. discussion 984-5
76. Montano AM et al. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. J Inherit Metab Dis. 2007;30(2):165–74.
77. Tomatsu S et al. Mutations and polymorphisms in GUSB gene in mucopolysaccharidosis VII (Sly Syndrome). Hum Mutat. 2009;30(4):511–9.
78. Tomatsu S et al. Mutation and polymorphism spectrum of the GALNS gene in mucopolysaccharidosis IVA (Morquio A). Hum Mutat. 2005;26(6):500–12.
79. Montano AM et al. Growth charts for patients affected with Morquio A disease. Am J Med Genet A. 2008;146A(10):1286–95.
80. Yabe H et al. Hematopoietic stem cell transplantation for Morquio A syndrome. Mol Genet Metab. 2016;117(2):84–94.
81. Cathey SS et al. Phenotype and genotype in mucolipidoses II and III alpha/beta: a study of 61 probands. J Med Genet. 2010;47(1):38–48.
82. Tiede S et al. Mucolipidosis II is caused by mutations in GNPTA encoding the alpha/beta GlcNAc-1-phosphotransferase. Nat Med. 2005;11(10):1109–12.
83. Paik KH et al. Identification of mutations in the GNPTA (MGC4170) gene coding for GlcNAc-phosphotransferase alpha/beta subunits in Korean patients with mucolipidosis type II or type IIIA. Hum Mutat. 2005;26(4):308–14.
84. Poorthuis BJ et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet. 1999;105(1–2):151–6.
85. Esposito S et al. Heparan N-sulfatase gene: two novel mutations and transient expression of 15 defects. Biochim Biophys Acta. 2000;1501(1):1–11.
86. Valstar MJ et al. Sanfilippo syndrome: a mini-review. J Inherit Metab Dis. 2008;31(2):240–52.
87. van de Kamp JJ et al. Genetic heterogeneity and clinical variability in the Sanfilippo syndrome (types A, B, and C). Clin Genet. 1981;20(2):152–60.
88. Metcalf JA et al. Mechanism of shortened bones in mucopolysaccharidosis VII. Mol Genet Metab. 2009;97(3):202–11.

Chapter 8
Autoimmune Diseases: Rheumatic Diseases

Definition

An autoimmune disease (AID) is characterized by tissue damage and caused by self-reactivity of different effector mechanisms of the immune system, namely, antibodies and T cells [16].

Etiology

Its occurrence may be associated with genetic and/or environmental predisposition. There is an activation of the adaptive immune response with tissue damage and inflammation in the absence of any infection, exposure to toxins, or tumor growth [16].

Prevalence

Although, individually, each AID affects a small number of individuals, as a whole, it is estimated that its prevalence is between 7.6% and 9.4% [17]. All AIDs, to some extent, have implications for fertility and obstetrics. Most AIDs occur frequently in women and should they appear at childbearing age, they pose a potential risk for almost all aspects of reproduction, from fertility to pregnancy itself [18–22]. These pregnancies are always high risk, often associated with fetal loss in the first trimester, preeclampsia/eclampsia, intrauterine growth restriction, premature rupture of membranes, placental insufficiency, preterm birth, caesarean delivery, and low birth weight [18, 19, 23].

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_8

The onset of many systemic autoimmune diseases, including systemic lupus erythematosus (SLE), occurs during childbearing years [24].

Treatment

Chemotherapy is often used for noncancerous conditions such as autoimmune diseases like systemic lupus erythematosus (SLE) and hematological diseases. Cyclophosphamide (CYC) treats severely active autoimmune disease, and it has significant gonadotoxic effects, decreasing the function of granulosa cells and impacting on fertility. Previous studies demonstrated that the cumulative dose and patient age at initiation of CYC are the most important predictors of ovarian failure [25–29]. Chemotherapy given before a girl undergoes puberty has little effect on menstrual patterns [24, 30].

CYC treatment in women with rheumatologic diseases increases the risk of premature cessation of menstruation, nulliparity, and infertility in this population [24].

In an effort to reduce exposure to CYC, several newer therapeutic options have been investigated for the treatment of severe manifestations of autoimmune diseases.

The use of CYC as induction therapy for lupus nephritis (LN) is declining since the introduction of induction therapy with mycophenolate mofetil (MMF), which may be an adequate initial therapy for mild LN, is well tolerated [31, 32] and is not associated with gonadotoxicity. A subset of LN patients may also respond to the "euro-lupus" regimen, consisting of six doses of 500 mg CYC given every 2 weeks, followed by azathioprine [33]. The resulting total CYC exposure of 3 grams is much lower than cumulative doses given in standard 6-month courses for LN. However, patients with severe proliferative LN with renal insufficiency, and those who do not respond initially to MMF, will still require standard monthly intravenous CYC therapy [34].

Use of the anti-CD20 monoclonal antibody, rituximab, may be an effective alternative to CYC in some patients with systemic vasculitis [34].

Adjunctive oral contraceptive use during gonadotoxic therapy has been proposed for the preservation of ovarian function, but convincing evidence regarding its efficacy for this purpose is lacking [34].

Fertility Preservation

In young patients treated with cytotoxic drugs, ovary protection before and during treatment is important, should be offered, and may help to preserve fertility [35] .

Fertility preservation options:

- Cryopreserving gametes
- Cryopreserving embryos
- Cryopreserving gonadal tissue
- There are options for fertility preservation that also prevent POI: GnRH-a

Progress in reproductive medicine has made it possible that women who undergo therapy with CYC for lupus nephritis, systemic sclerosis, or vasculitis can preserve their fertility [36]. Hormonal methods may be prescribed during CYC therapy in an attempt to preserve ovarian function. The use of gonadotropin-releasing hormone agonists (GnRH-a) during CYC therapy is increasingly advocated for use in rheumatic and some oncologic diseases [34, 37–40].

GnRH-a may simulate a prepubertal state during chemotherapy, thus preventing damage to maturing follicles. GnRH-a treatment is protective against ovarian failure after CYC by decreasing but not completely eliminating ovarian damage [24, 40–42].

Effect on Fertility and Reproduction

Family planning is an important issue for patients with rheumatic diseases [35]. Patients with inflammatory joint diseases such as RA or SpA as well as patients with collagenous diseases such as SLE have a reduced number of children.

Several factors may contribute to this:

- Personal choice.
- Age-related fertility decline.
- Uncertainty of patients and consulting doctors.
- Impaired sexual function due to pain or fatigue may play a role.
- Frequently used medication side effects have a negative influence on conception and fertility, either directly or indirectly, by affecting patients' sexual desire or quality of life [43].
- Decreased ovarian reserve.
- Systemic inflammation.
- Psychosocial causes, such as decreased sexual desire or simply personal choice.

While recent studies have found reduced AMH levels or antral follicle counts in patients with SLE, Takayasu arteritis, Behcet's disease (BD), and primary APS, other groups were unable to demonstrate a reduction in ovarian reserve measured by AMH in patients with early RA or Crohn's disease and RA [35, 43].

Rheumatic Diseases

Systemic Lupus Erythematosus

Prevalence

Lupus affects approximately 1.5–2 million Americans and is ten times more common in women than in men. In fact, >90% of Americans diagnosed with lupus are women, and it is estimated that 1 in every 2000 women have lupus [1].

Natural History

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with characteristic exacerbations and remissions that affects multiple organ systems [2]. It can affect the skin, joints, kidneys, brain, and other organs. The underlying cause is unknown.

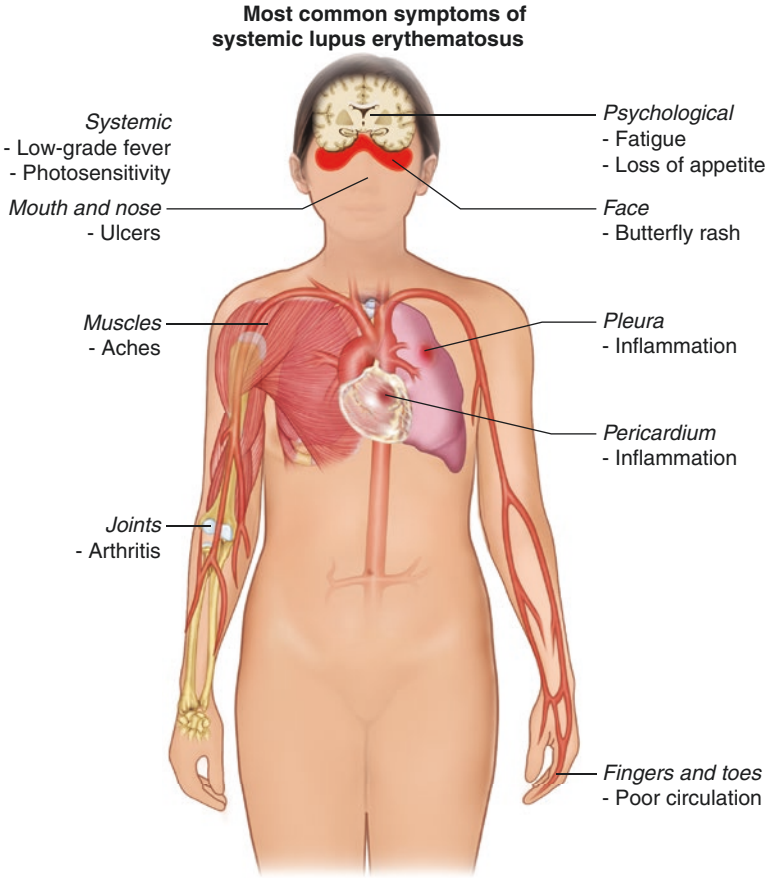
Disease Presentation

The symptoms of SLE [2, 3] include:

- Joint pain and swelling
- Arthritis
- Chest pain
- Fever with no other cause
- General discomfort, uneasiness, or ill feeling
- Hair loss
- Mouth sores
- Sensitivity to sunlight
- Skin rash
- Swollen lymph nodes
- Vaginal ulcers
- Fatigue
- Depression

Other symptoms depend on which part of the body is affected.

- Brain and nervous system: headaches, numbness, tingling, seizures, vision problems, and personality changes
- Digestive tract: abdominal pain, nausea, and vomiting
- Heart: arrhythmias
- Lung: coughing up blood and difficulty of breathing
- Skin: patchy skin color and Raynaud's phenomenon



Effect on Female Fertility

Menstrual Disturbances

Many women with SLE experience menstrual disturbances ranging from amenorrhea to menorrhagia [4]. Women who receive anticoagulation therapy for thrombotic complications may experience menorrhagia. Amenorrhea may occur as the result of cyclophosphamide (CYC) treatment, which can cause ovarian failure, but also as a result of the disease itself. Amenorrhea in women with SLE is also associated with anti-corpus luteum antibodies with raised FSH levels, suggestive of an autoimmune SLE-related menstrual dysfunction [5]. Pasoto

et al. (2002) found 53% of adult women under the age of 40 years with SLE had menstrual irregularity in the absence of alkylating agents [6]. Those with high disease activity were found more likely to have menstrual disturbances than those with less disease activity.

Reproductive System Impairment
Impairment of the reproductive system of women with SLE may result due to disease activity, autoantibodies, and through iatrogenic cytotoxic treatments [4, 7]. Impairment of the reproductive system may cause:

- Problems preventing successful fertilization thus leading to infertility
- Obstacles in effective implantation to the uterine wall
- Difficulties in maintaining pregnancy post-implantation
- Complications during labor

Drug-Related Infertility
Despite improvements in the treatment options for SLE, the disease can be therapeutically challenging for rheumatologists. Patients with acute exacerbations with severe organ manifestation may need cyclophosphamide (CYC). CYC is an alkylating chemotherapeutic agent shown to cause premature ovarian insufficiency (POI) and deplete healthy oocytes [4, 8]. Its toxicity is associated with many secondary risk factors, including the cumulative dose of CYC, the age at which the drug is administered, history of thyroid disease, disease duration, and presence of anti-Ro and anti-U1RNP antibodies [4, 8, 9]. Therefore, CYC should be prescribed at the lowest effective dose possible and for the shortest duration, particularly in older women. Boumpas et al. (1993) found that 17% of patients under age 25 years with ≥15 cycles of CYC developed POI. Of those over the age of 30 years, 100% developed POI [10].

Antiphospholipid Antibody Syndrome (APS)
Approximately 30% of women with SLE also have antiphospholipid antibody syndrome (APS) or Hughes syndrome. Traditionally, APS is known for causing spontaneous abortions, stillbirths, and premature births. However, APS can lead to venous and arterial thrombotic events, which may restrict the blood supply to reproductive organs, thereby affecting fertility. APS should be considered a risk factor for infertility in women with SLE [4].

Lupus Nephritis
Approximately 30–75% of women with SLE, dependent on ethnic and racial background, develop lupus nephritis chronic renal failure. Women with chronic renal failure are likely to develop infertility through hypothalamic–pituitary dysfunction, because renal failure and/or hemodialysis tends to raise prolactin levels—which reduces the production of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Women with lupus nephritis tend to have menstrual irregularity with anovulatory cycles [4].

Effect on Male Fertility

Reproductive System Impairment

Impairment of the reproductive system in men with SLE may result due to disease activity, autoantibodies, and through iatrogenic cytotoxic treatments [4, 7]. Impairment of the reproductive system may be due to problems preventing successful fertilization, thus leading to infertility, such as testicular failure and sperm abnormalities. The degree of sperm abnormalities has been correlated with a significant reduction in testes volume in men with SLE, as determined by ultrasound imaging. This is most likely due to damage to the seminiferous tubules [11].

Drug-Related Infertility

Despite improvements in the treatment options for SLE, the disease can be therapeutically challenging for rheumatologists. Patients with acute exacerbations with severe organ manifestation may need cyclophosphamide (CYC). CYC is an alkylating chemotherapeutic agent shown to impair spermatogenesis. In boys treated with postpubertal CYC therapy, sperm quantity and quality were significantly impaired compared to health controls. CYC is associated with reduced Leydig cell count and reduced testosterone levels [4].

Methotrexate (MTX) and sulfasalazine (SSZ) can also reduce sperm count and may cause infertility in males [4].

Autoimmune Orchitis

Approximately 40% of men with SLE have autoimmune orchitis, which often causes male infertility and is characterized by the presence of specific antisperm antibodies (ASA), with limited sperm abnormalities [12].

Klinefelter Syndrome

Men with SLE are 14 times more likely to have Klinefelter syndrome than healthy males [13]. Men with Klinefelter syndrome have low testosterone with high FSE and LH levels and are typically infertile. Fertility may be restored in these men by surgical removal of sperm and IVF therapy.

Fertility Preservation Options for Women

Gonadotrophic Receptor Hormone Agonist

Leuprolide, a gonadotrophic receptor hormone (GnRH) agonist, is protective against POI when administered 10–14 days before each CYC pulse. Leuprolide causes a drastic reduction in estrogen and progesterone levels, which significantly reduces the risk of POI in patients with SLE from 30% to 5% [14].

Oocyte or Embryo Cryopreservation

Oocyte and embryo cryopreservation are the most effective methods to preserve fertility; however, in women with SLE, hormonal manipulation may trigger

exacerbation of SLE as a result of raised estrogen levels following ovarian stimulation. Exogenous estrogen therapy is also associated with an increased risk of thrombosis. The safest approach is to avoid overt ovarian hyperstimulation syndrome (OHSS), administer coadjuvant therapy, and use natural E(2) or P through non-oral route [4].

Ovarian Tissue Cryopreservation
One entire ovary is removed surgically, and the outer surface (cortex), which contains the eggs, is frozen in strips for later use. Women who have undergone CYC can have pieces of the tissue thawed and transplanted back. A number of pregnancies have resulted from using this technique.

Fertility Preservation Options for Men

Sperm Banking
Sperm cells are collected and frozen for future use.

Testicular Tissue Banking
The testicular tissue, including cells that produce sperm and sperm itself, is removed and frozen. The procedure has varying risks and side effects. These options may not be appropriate for many patients.

Testosterone
Testosterone can be administered to maintain spermatogenesis in men undergoing CYC treatment for SLE. Studies have shown that 100 mg i.m. fortnightly can preserve fertility while on CYC [15]. The testosterone is effective at preserving fertility because it reduces endogenous gonadotrophin release.

Fertility Preservation Expert Opinion

Henes et al. (2012)
SLE patients are young and have an excellent response to treatment as well as long-term survival. The Henes et al.'s (2012) FertiPROTEKT study enrolled 68 women with SLE, with an average patient age of 25, and 91.2% of these participants did not have children. Of the 68 women enrolled, only 5 chose not to preserve fertility prior to CYC treatment. Of those who did elect to preserve fertility, 91.2% had GnRH analogue treatment and 25% cryopreserved ovarian tissue, of which 4.4% retrieved and froze oocytes. Henes et al. (2012) made fertility preservation recommendations for women with SLE based on study results and literature review:

- All women after menarche and less than 40 years of age who receive CYC for SLE or any autoimmune disease should be counseled by a doctor trained in reproductive medicine on fertility preservation methods, in agreement with a responsible rheumatologist.

- The use of GnRH analogues prior to CYC treatment can be recommended for all patients up to the age of 40 years.
- GnRH administration can be combined with ovarian tissue cryopreservation, especially in patients under the age of 35 years.
- Stimulation therapy and subsequent cryopreservation of oocytes or embryos should be critically evaluated. In the case of advanced age and urgent desire to conceive, as well as maintained by disease activity and associated diseases, this method is still the most effective at preserving fertility.

Rheumatoid Arthritis (RA)

Epidemiology

RA is the most common chronic inflammatory joint disease, affecting 0.5–1% of the populations in the industrialized world and women more frequently than men (2–3:1) [44–47]. However, in certain Native American populations, the prevalence is much higher [44, 47].

Etiology

Causes of the disease are unknown, but environmental factors play an important role:

1. RA has been regarded as a disease of the poor, and lower levels of education and upbringing under adverse socioeconomic conditions are afflicted with a more severe course of RA and/or a higher baseline inflammatory state [44].
2. Smoking may increase the risk and possibly also the severity of RA and is associated with increased tumor necrosis factor (TNF) and autoantibody production which in turn is related to genetic factors characteristic of RA [48–50], although these associations have not been confirmed in all populations [44, 51].
3. The microbiome appears to play an important role in experimental forms of arthritis [44, 52, 53], and it is conceivable that this is also the case in man, especially given the increased prevalence of periodontitis [44].

Genetic Features

One of the major indications for a genetic predisposition to a disease is its increased familial occurrence. While in RA the prevalence in the general population is 0.5–1%, it rises to 2–4% in siblings and about 15% in identical twins [54, 55].

Clinical Manifestations

Pain and swelling of the joints

Clinical synovitis (swelling due to synovial involvement) in at least one joint [56]. The more joints that are affected (swollen or painful), the easier the patient can fulfill the criteria. Joints involved are primarily those of the wrists, fingers, and toes [57]. RA synovitis leads to subchondral bone erosions and damage to cartilage and thus to the totality of the *pathology* of RA which can culminate in completely destroyed joints, as seen clinically and upon imaging, especially by radiography [44].

Diagnosis

Autoreactivity, in association with a genetic predisposition, appears to play a major role in pathways to RA, and the presence of autoantibodies is associated with joint damage and thus of prognostic in addition to diagnostic value [44].

The immunologic hallmark of RA is the presence of autoantibodies in the circulation and in the synovial fluid.

Autoantibody rheumatoid factor (RF)

RF is found in up to 80% of RA patients, and, as indicated before, a pathogenic role of RF must be assumed. RF levels change quite rapidly with changes in disease activity and decrease with effective therapy [44].

- Anti-citrullinated protein antibodies (ACPA) are more predictive of RA, associated with a bad outcome, and more specific for RA than RF [44].

The most important autoantibodies in RA are RF and ACPA. They are both important components in classification criteria and therefore of diagnostic help [44]. Their sensitivity and specificity for the diagnosis of RA are similar (sensitivity about 50–60%, specificity about 85–95%) [44]. Both of these autoantibodies fluctuate with disease activity and effective therapy [58].

Effect on Fertility

The impact of high RA disease activity on fertility could be mediated via:

- Inflammatory mediators, since many cytokines, chemokines, and growth factors play an important role in the [59] preimplantation blastocyst–endometrial interactions [60]. Although research is identifying important roles that prostaglandins and cytokines may play in the reproductive cycle, it is still unclear what the clinical impact is in systemic inflammatory diseases, such as RA [43].

- The use of NSAIDs. NSAIDs may interfere with ovulation, implantation, and placentation through inhibition of prostaglandin synthesis [61–63]. Selective COX-2 inhibitors seem to inhibit ovulation more potently than traditional nonselective NSAIDs. However, this finding is only based upon case reports or small case series [59, 61].
- The use of prednisone prolongs the TTP. Glucocorticoids in therapeutic dosages have been shown to decrease luteinizing hormone pulse frequency from the pituitary gland [64, 65].

It should be recommended that RA patients trying to conceive should strive for low disease activity, thereby avoiding NSAIDs and daily dosages of prednisone exceeding 7.5 mg [59].

Medications and Infertility

Iatrogenic causes of infertility may contribute to the smaller family size of RA patients. Although, the relationship between RA and subfertility is complex [43].

While data suggests an increase in infertility in women with RA, the cause for this is unknown. It could be related to advanced maternal age, personal choice, decreased sexual activity, inflammatory cytokines, medications, or a combination of mentioned factors.

While research progresses to identify the cause of infertility, there are some specific suggestions that physicians follow to help patients with RA and infertility.

In addition to avoiding NSAIDs while attempting conception, consideration of referral to a reproductive endocrinologist may prove helpful. Fortunately, reproductive technologies may be available to women with RA [43].

No good studies have been performed on the fertility of male patients with RA and the impact of their disease on the pregnancy outcome of their partners. Lower testosterone levels have been described in male patients with RA than in healthy controls [66], but whether this also results in less fertility is not known. In addition, little is known on the effects of antirheumatic drugs and medication [43].

Vasculitis

Vasculitis is an immune-mediated disease potentially fatal, especially when it affects medium or large caliber vessels.

There are three categories of systemic vasculitis:

Large, medium, and small vessel vasculitis

Accurate diagnosis requires clinical, pathological, and laboratory data, crucial for diagnosis and therapy.

This disease can cause aneurysms, ruptures, and hemorrhages, and also, it may lead to luminal stenosis with obstruction, tissue ischemia, or infarction.

Behcet's Disease (BD)

Definition

BD is a multisystem vasculitis [16]. It is a systemic inflammatory disease of unknown etiology and autoimmune pathogenesis [67].

Clinical Manifestations

- Orogenital ulcers.
- Uveitis.
- Skin lesions.
- It may also affect the gastrointestinal tract, joints, the central nervous system, or the cardiovascular system.
- Venous or arterial thrombosis may occur due to endothelial dysfunction and hypercoagulability [16].

Diagnosis

Its diagnosis is primarily clinical.

Treatment

Treatment may be topical (corticosteroids) or systemic (corticosteroids, anti-TNF-α) [16, 67, 68].

Autoimmune Thyroiditis (AIT)

Definition

Ninety percent of non-iatrogenic hypothyroidism in countries without iodine deficiency occurs due to autoimmunity, and it is a prevalent condition in women of childbearing age.

There are several types of AITs, of which the most noteworthy is Hashimoto's thyroiditis.

TAI (thyroid autoimmunity) is the leading cause of hypothyroidism, which itself negatively affects the course of pregnancy [69, 70].

Diagnosis

High levels of antithyroglobulin and antithyroid peroxidase antibodies in the presence of hypothyroidism or not

Epidemiology

Prevalence ranges between 8% and 14%. This is the most frequent autoimmune condition and the first cause of thyroid dysfunction among women of reproductive age [69, 71, 72].

Treatment

Available treatment consists of hormone replacement with exogenous thyroxin.

Effect on Fertility

Combining these data suggest a significantly higher incidence of thyroid antibodies in infertile women compared to controls [69]. An association has been particularly observed in women with endometriosis and ovarian causes of infertility, i.e., polycystic ovary syndrome and premature ovarian failure (POF) [69, 73–75]; the pathogenic mechanisms underlying the relationship between the presence of TAI and infertility remain largely speculative. A reduction in the local availability of T3 might thus have a detrimental impact on the normal female reproductive function [69].

Antiphospholipid Syndrome

Definition

APS is an acquired thrombophilic disorder in which autoantibodies are produced to a variety of phospholipids and phospholipid-binding proteins [76, 77]. It is a systemic autoimmune condition characterized by vascular thrombosis and/or pregnancy morbidity.

Classically, a differentiation between primary and secondary APS has been made, with the latter being related to several pathologic conditions, such as autoimmune diseases (SLE, rheumatoid arthritis), infection (leprosy, parvovirus B19, human immunodeficiency virus [HIV], hepatitis C, cytomegalovirus), hematological diseases, hemodialysis, malignancy, and drugs (hydralazine, phenytoin, quinidine, cocaine) [78].

Prevalence

APS is more common in women, with a female-to-male ratio of 5:1 and a mean age at diagnosis of 31 years (15–85 years) [79]. The risk of thrombosis ranges from 0.5% to 30% [80]. The prevalence of both lupus anticoagulant and ACAs is about 1–5% in healthy young subjects [76].

Clinical Criteria for Diagnosis

- Vascular thrombosis of any vessel in any tissue or organ.
- Pregnancy morbidity:
  - Three unexplained consecutive spontaneous abortions (<10th week of gestation)
  - One fetal death more than 10 weeks , morphologically normal fetus
  - One premature delivery of morphologically normal neonate <34th week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency [78]

Laboratory Diagnostic Criteria

1. Positive plasma lupus anticoagulant (aPL), revealed by delayed clotting in phospholipid-dependent coagulation tests on two or more occasions at least 12 weeks apart [78].
2. Moderate to high titers of anticardiolipin antibodies (IgG or IgM); on two or more occasions at least 12 weeks apart, low levels may be observed in 3–5% of normal individuals and are of uncertain significance.
3. More recently, a high titer of antibodies IgG or IgM to β2-glycoprotein 1 on two or more occasions is also considered sufficient to establish the diagnosis [42, 77, 78].

Disease Presentation

aPL provides the most frequent acquired risk factor for pregnancy complications.

Evidence implicates antiphospholipid antibodies as a predisposing factor in recurrent pregnancy loss; in these patients the thrombogenic changes of pregnancy exaggerate an inherent predisposition to thrombosis resulting in reduced uteroplacental blood flow, placental thrombosis, and pregnancy loss [78].

A small but still important number of women with recurrent pregnancy loss have circulating antiphospholipid antibodies [78, 81]. Women with antiphospholipid antibodies identified by screening in early gestation have an increased rate of pregnancy loss [78, 82, 83]. They also exhibit an unusually high rate of loss in subsequent pregnancies, even when treated [78, 84–86].

Antiphospholipid syndrome can be found in association with systemic lupus erythematosus or in women with no other evidence of autoimmune disease [78, 87–89].

Frequently, fetal death is preceded by observations of poor fetal growth, oligohydramnios, heart rate abnormalities, and preeclampsia or eclampsia, all of which might reflect hypoxemia resulting from placental insufficiency [78].

Pathogenesis

Antiphospholipid antibodies are directed against platelets (promoting adhesion) and the vascular endothelium (where alterations in prostacyclin/thromboxane metabolism cause vasoconstriction) [78, 83, 84], both mechanisms predisposing to thrombosis [78].

The pathogenesis of obstetric antiphospholipid syndrome (OAPS) is rather heterogeneous, complex, and not fully understood yet [36].

Abnormal endovascular trophoblast invasion could explain early miscarriages in women with antiphospholipid syndrome and, in less severe cases, the development of later pregnancy complications relating to uteroplacental vascular insufficiency. The pathophysiology involves inflammation at the maternal-fetal interface, preventing normal trophoblast development and function [78].

Diagnosis

Antiphospholipid syndrome is an autoimmune disorder having specific clinical and laboratory features; diagnosis requires at least one of each.

- Antiphospholipid antibodies (aPL) are the serological markers of the antiphospholipid syndrome (APS) [90].
- The clinical diagnostic criteria include thromboembolic events (arterial, venous, small vessel) and pregnancy loss, fetal death after 10 weeks, and premature birth at less than 34 weeks associated with severe preeclampsia or placental insufficiency [78].

(International Consensus Definition for the Diagnosis of Antiphospholipid Syndrome)

Diagnosis requires one of the clinical criteria and one of the laboratory findings.

Although the prevalence of antiphospholipid syndrome among all women with recurrent pregnancy loss is quite low (3–5%) [78], the disorder is nonetheless a potentially treatable cause of recurrent pregnancy loss. Tests for the detection of a lupus anticoagulant and antiphospholipid antibodies specified above are minimally invasive, relatively inexpensive, and, therefore, justified in the evaluation of most if not all women with recurrent pregnancy loss [78].

Many apparently healthy women have low levels of circulating antiphospholipid antibodies [78, 81, 91–93].

Disease Management

Typical combined treatment regimen includes aspirin (75–85 mg/day), beginning with attempts at conception, and unfractionated heparin (5000–10,000 subcutaneous twice daily), beginning at first indication of pregnancy. Live birth rates for women with antiphospholipid syndrome who receive combined treatment with aspirin and unfractionated heparin during pregnancy (70–80%) are much improved over those observed in women who receive aspirin treatment or no treatment (20–40%) [78, 94–98]; treatment does not eliminate the high risk for pregnancy complications (preterm labor, premature rupture of membranes, intrauterine growth restriction and fetal demise, preeclampsia, and placental abruption) and poses additional risks for the mother (gastric bleeding, osteopenia) [78, 95, 96]. Low-molecular-weight heparin interventional trials among women with recurrent pregnancy loss and antiphospholipid syndrome and other acquired thrombophilias suggest it is both safe and effective [78, 86, 99–101].

Effect on Fertility

Women with APS or repeatedly positive aPL who are undergoing ovulation induction (controlled ovarian hyperstimulation) are candidates for thromboprophylaxis based on the known elevation of 17β-estradiol in this setting [36].

There are no data to support the inclusion of infertility as criteria for APS, and investigation of aPL in patients with infertility should not be done in routine clinical practice.

There are no well-designed studies to show that patients with infertility and positive aPL require treatment (e.g., with heparin compounds) to improve IVF outcome per se, and the association of aPL with infertility does not appear to be causative [78]. On the other hand, given the deleterious effects played by aPL on gestation, it has been postulated that these autoantibodies might be involved in infertility [90, 102].

The American Society for Reproductive Medicine, in a critical review published in 2008, concluded that aPL positivity is not associated with a reduced success of assisted reproduction, thus not justifying aPL screening nor treatment of infertile subjects [90, 103].

The presence of antiphospholipid antibodies does not seem to affect ART outcome, and therefore therapy is not justified.

In women affected by SLE or APS, ovarian stimulation seems to be safe and successful when the disease is in clinical remission, and appropriate prophylactic anticoagulant or anti-inflammatory therapy is administered. However, the most dangerous period is pregnancy, in which the rates of fetal and maternal complications are high.

The high risk for pregnancy loss in women with SLE and increased aPL, especially lupus anticoagulant (LA), was demonstrated in several studies [36, 79].

Reproductive failure is a heterogeneous condition that can be related in several autoimmune diseases to immunological pathomechanism [18]. Beside the great role played by innate immunity, several autoantibodies have been associated with impaired fertility.

Above all, the aPL including LA, anticardiolipin (aCL), and anti-β2 glycoprotein I (aβ2GP1) have all been reported to be associated with recurrent pregnancy loss (RPL) or as possible factors involved in infertility [104], more related to pregnancy loss.

Ovarian stimulation can result in high concentrations of estradiol, exceeding physiological levels, with a risk for ovarian hyperstimulation syndrome (OHSS) resulting in a capillary leak syndrome and raised hematocrit which increases the risk of thrombosis [105, 106].

The risk can be reduced by using stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonists and ovulation induction with GnRH agonists which almost completely avoids ovarian hyperstimulation syndrome.

This protocol requires a cryopreservation of all fertilized oocytes and an interval of at least 1 month before embryo transfer. Friendly ovarian stimulation, single-embryo transfer, avoidance of OHSS, administration of coadjuvant therapy, and the use of natural estrogen or progesterone through a non-oral route may constitute the safest approach [77].

Active SLE, badly controlled arterial hypertension, pulmonary hypertension, advanced renal disease, severe valvulopathy or heart disease, and major previous thrombotic events are situations on which to discourage ART [36, 107].

Sjögren's Syndrome

Definition

Sjögren's syndrome (SS) is a complex heterogeneous disease characterized by a broad spectrum of clinical and serological manifestations, including non-Hodgkin lymphoma (NHL) [108]. SS may occur either alone as a primary process (primary SjS) or in association with other autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic scleroderma (SScl).

Incidence

Diagnosed in about 0.5–1% of the general population, SS represents one of the most common systemic autoimmune diseases [109], with a prevalence of 60.82 cases per 100,000, usually in middle-aged females (female/male ratio 9:1) having a peak incidence in women aged between 55 and 65 years [108, 110].

Pathogenesis

Both genetic and non-genetic factors are involved in disease susceptibility and initiation of disease process [108].

The disease is characterized by lymphocytic infiltration of exocrine (mainly salivary and lachrymal) glands and tissue destruction [111].

Etiology

SjS etiology remains unknown; interplay of environmental factors (such as viruses, stress, or hormonal factors) with the host's specific genetic background can lead to aberrant immune responses, chronic inflammation, destruction of the affected tissue, and ensuing ocular and oral dryness [111]. Epithelium, the principal target of SjS, has been indicated to be an active participant [112].

Clinical Manifestations

Wide spectrum of clinical features ranging from mild local symptoms (dry mouth and dry eyes) to systemic manifestations. About 5–8% of patients develop non-Hodgkin lymphoma.

Local manifestations arising from salivary and lachrymal gland involvement are considered the typical SjS-related features; any other organ system can be affected in the setting of SjS giving rise to systemic manifestations. Mouth and eye dryness are the most characteristic features of SjS [111].

The majority of SjS patients display an indolent benign course, and in the vast majority of patients, the glandular sicca features and serologic profile remain unchanged during disease course [111, 113, 114].

Systemic manifestations (beyond salivary and lachrymal glands):

- *Musculoskeletal* non-erosive arthritis affecting the small joints and intermittent synovitis. Myalgias, fibromyalgia-like features, and chronic fatigue are also observed [115].
- *Raynaud's phenomenon*: affects approximately 30–50% of primary SjS patients[116].
- *Respiratory tract involvement*: usually mild and include dry cough as a result of desiccation of tracheobronchial tree [111].
- *Gastrointestinal and hepatobiliary manifestations*: dysphagia and liver manifestations are usually mild. Primary biliary cirrhosis (PBC) is the commonest type of liver involvement [111].
- *Renal involvement*: two types of renal abnormalities related to SjS, tubulointerstitial nephritis and glomerulonephritis [111].
- *Vasculitis:* observed in about 15% of SjS patients [111].

- *Neuropsychiatric involvement*: prevalence of peripheral neuropathy in SjS varies from 2% to 60%. The most common types of peripheral nerve involvement in primary SjS are sensory, small fiber neuropathy (SFN), and sensorimotor neuropathy [95].
- *Endocrine involvement*: autoantibodies against organ-specific autoantigens of endocrine glands such as thyroid, adrenals, and ovaries have been previously documented at higher rates (in approximately one-fifth of patients) compared to healthy individuals [111].
- *Lymphoproliferative disease*: non-Hodgkin lymphoma (NHL) is encountered in about 5–8% of SjS patients and is usually of indolent course [111].

Diagnosis

Combined clinical, pathologic, and serologic assessment of patients can easily lead to the diagnosis.

- Diagnosis requires the presence of either focal lymphocytic infiltrates in minor salivary glands or anti-SSA/SSB autoantibodies [111].
- B-cell hyperactivity is considered as a disease hallmark as evidenced by the presence of hypergammaglobulinemia and serum autoantibodies, both specific and nonspecific. These include—among others—antinuclear antibodies against ribonucleoproteinic complexes Ro/SSA and La/SSB, rheumatoid factor (RF), and cryoglobulins [111].
- Ultrasonography, conventional magnetic resonance imaging, and magnetic resonance sialography may provide useful, noninvasive diagnostic alternatives [111].
- Parotid gland enlargement (PGE) is a relatively common manifestation of SjS. It is usually bilateral, firm to palpation, asymptomatic, and considered as an adverse prognostic factor for lymphoma development [111].

Differential Diagnosis

Differential diagnosis should consider various medical conditions that may cause mucosa dryness.

Treatment

Treatment of SjS is directed to provide symptomatic relief and to recognize and treat disease complications:

- Eye lubricants are the mainstay of treatment.

- Systemic therapeutic intervention: based on the severity of extraglandular manifestations. Nonsteroidal anti-inflammatory drugs and/or hydroxychloroquine may be administered for arthralgias/myalgias and methotrexate for persistent arthritis.
- Corticosteroids are mainly employed for severe extraglandular manifestations [111].
- Aggressive treatment with cytotoxic drugs carries an increased risk for lymphoma development and should be reserved for threatening systemic manifestations.

Effect on Fertility

The disease will have an effect on fertility only if it requires cytotoxic treatment.

Scleroderma

Definition

Scleroderma is derived from the Greek word *skleros* which means hard and *derma* which means skin. This is a chronic autoimmune, systemic, potentially lethal, connective tissue disease characterized by vasculopathy, immunological abnormalities, and excessive fibrosis that involves the skin and internal organs such as the lungs, heart, gastrointestinal tract, and kidneys [76, 77].

Epidemiology

Prevalence of SSc in the United States is 27.6 per 100,000 [77]. It is a relatively rare disease typically presenting in the fifth or sixth decade. Scleroderma is three times more frequent in women than men [78], and this gender difference is heightened during the reproductive years (ages 15–50), during which females are afflicted 15-fold more [76, 79].

Ethiopatogenia

The etiology is still unclear; epidemiologic studies indicate a complex mix of genetics and environment which predispose to phenotypic disease [77].

Pathogenesis of scleroderma includes vascular dysfunction, mononuclear-mediated inflammation, and connective tissue fibrosis [76].

However, various environmental and/or genetic factors are thought to trigger complex pathogenic mechanisms that interact with each other at different levels.

Clinical Manifestations

Early symptoms of SSc are nonspecific:

Majority of patients develop Raynaud's phenomenon (RP) for variable periods of time before the appearance of skin changes. Fatigue, joint pain, and hand swelling develop early in the disease. Esophageal dysmotility, manifested as gastroesophageal reflux disease (GERD) or dysphagia, is also among the early features of SSc [77].

Progressive connective tissue disease is associated with significant changes in appearance including skin discoloration and/or hardening, skin tightening around the mouth, finger lesions, and in some cases digit amputation. These facial and bodily changes bring afflicted women to report an elevated body image dissatisfaction, even compared to severe burn patients [76, 80]

Swelling and tightening of the skin and other connective tissues are the hallmark of scleroderma and can be localized or systemic.

Linear scleroderma and morphea are examples of the *localized subtype*, where the pathology is confined to the skin.

Involvement of the internal organs in addition to the skin is called *systemic sclerosis* (SSc) [77].

The affected skin displays a spectrum of changes starting with edema, typically on the hands and fingers, progressing through a shiny, thick, sclerotic skin that is tightly fixed to the underlying structures with loss of hair and sweat glands and ending with an atrophic tethered skin. Areas of hypo- and hyperpigmentation may develop, giving a salt-and-pepper appearance. Telangiectasias and calcinosis may also occur.

Severe vasospasm and vascular occlusive changes can lead to ulceration, infarction, and gangrene of the digits [77]. Those, as well as the gastrointestinal (GI) complications, interstitial lung disease, pulmonary hypertension, and renal involvement, are responsible for the morbidity and mortality in SSc.

Systemic sclerosis can display severe organ involvement that develops early in the disease. For this reason, patients should be monitored closely during the first 3–4 years of the disease for the signs and symptoms of visceral involvement [77].

Late age of onset, the diffuse cutaneous subset, anti-Scl-70 positive antibody, and cardiopulmonary involvement are associated with a poorer prognosis [77].

Diagnosis

SSc is associated with the presence of several autoantibodies, some of which may play a role in the pathogenesis of SSc and others appear to have diagnostic and prognostic value.

Effect on Fertility

The reduced self-esteem and altered body image may adversely affect the ability of scleroderma patients to form social and sexual relationships. The disease poses further difficulties to interpersonal relationships due to vaginal dryness and dyspareunia which afflicts up to 37% of patients [81] as well as arthritic involvement and joint contractures which may prevent sexual intercourse [76].

Steen et al. [82] found a similar rate of pregnancy and conception compared with normal controls. [76]

Autoimmune Polyglandular Syndromes (APS)

Definition

These are disorders characterized by autoimmunity against two or more endocrine organs.

APS are rare, inherited disorders that may appear throughout the life cycle [83].

Epidemiology

Like most autoimmune diseases, a female preponderance is present, with a female/male ratio of approximately 3:1. [84, 85].

APS Type I

It typically involves the adrenal and parathyroid glands, and a defect in cellular immunity, most often manifested by mucocutaneous candidiasis, is common.

Characteristically occurs in infancy or early childhood, with nearly all cases appearing before age 15

Other autoimmune disorders occurring less frequently in APS type I include autoimmune ovarian failure (approximately 60%), autoimmune gastritis with pernicious anemia, diabetes mellitus type 1, autoimmune thyroiditis, alopecia, vitiligo, and celiac disease [84, 85].

APS Type II

Schmidt's syndrome (adrenal and thyroid components present)

Carpenter's syndrome (autoimmune adrenal, thyroid, and pancreatic *B*-cell involvement are present)

Classically occurs in late childhood through adulthood, with a peak incidence around age 35. Several other autoimmune components (including non-endocrine diseases) may coexist with APS type II, including alopecia, vitiligo, pernicious

anemia, myasthenia gravis, autoimmune thrombocytopenic purpura, Sjögren's syndrome, and rheumatoid arthritis [85].

POF is infrequent in type II APS, with a reported incidence between 4% and 10% [85].

APS Type III

Differs from type II in that autoimmune adrenalitis (AD) is absent

Autoimmune POF has been reported in up to 60% of women with APS type III [85].

APS Type IV

The miscellaneous category (labeled "APS type IV" by Betterle et al. [85]) includes both endocrine and non-endocrine autoimmunities not falling into one of the other categories [84, 85].

AD may be a manifestation of APS type IV. [83]

Effect on Fertility

Those diagnosed with APS, particularly types I and III, could be offered serial screening for antibodies.

It seems logical to screen preadolescent and reproductive-aged women with a single autoimmune endocrinopathy for other autoimmune disorders, particularly when physical examination suggests subtle findings of other autoimmune disorders. Such screening may spare the patient significant morbidity and mortality associated with the untreated secondary autoimmune disorder (especially AD, hypoparathyroidism, and diabetes mellitus type 1) [83].

Appropriate counseling and referral to tertiary centers for high-dose corticosteroid treatment, ovarian tissue cryopreservation, or IVF could be contemplated before the prognosis for fertility becomes particularly affected [83].

References

Rheumatic Diseases

1. The Lupus Foundation of America. www.lupus.org.
2. Hirshfeld-Cytron J, Gracia C, Woodruff TK. Nonmalignant diseases and treatments associated with primary ovarian failure: an expanded role for fertility preservation. J Womens Health (Larchmt). 2011;20(10):1467–77. doi:10.1089/jwh.2010.2625.
3. Systemic lupus erythematosus. 2014. Medline Plus. http://www.nlm.nih.gov/medlineplus/ency/article/000435.htm.

4. Hickman R, Gordon C. Causes and management of infertility in systemic lupus erythematosus. Rheumatology. 2011;50(9):1551–8.
5. Pasoto S, Viana V, Mendonca B, Yoshinari N, Bonfa E. Anti-corpus luteum antibody: a novel serological marker for ovarian dysfunction in systemic lupus erythematosus? J Rheumatol. 1999;26:1087–93.
6. Pasoto S, Mendonca B, Bonfa E. Menstrual disturbances in patients with systemic lupus erythematosus without alkylating therapy: clinical, hormonal, and therapeutic associations. Lupus. 2002;11:175–80.
7. Velarde-Ochoa M, Esquivel-Valerio J, Vega-Morales D, Skinner-Taylor C, Galarza-Delgado D, Garza-Elizondo M. Anti-mullerian hormone in reproductive age women with systemic lupus erythematosus. Reumatol Clin. 2014;11(2):78–82.
8. Mok C, Lau C, Wong R. Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. Arthritis Rheum. 1998;41:831–83.
9. Henes M, Henes J, Neunhoeffer E, Von Wolff M, Schmalzing M, Kotter I, Lawrenz B. Fertility preservation methods in young women with systemic lupus erythematosus prior to cytotoxic therapy: experiences from the FertiProtekt network. Lupus. 2012;21(9):953–8.
10. Boumpas D, Austin H r, Vaughan E, Yarboro C, Klippel J, Balow J. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Ann Intern Med. 1993;119:366–9.
11. Soares P, Borba E, Bonfa E, Hallak J, Correa A, Silva C. Gonad evaluation in male systemic lupus erythematosus. Arthritis Rheum. 2007;56:2352–61.
12. Carp HJ, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. J Autoimmun. 2012;38(2–3):J266–74.
13. Scofield R, Bruner G, Namjou B, Kimberly R, Ramsey-Goldman R, Petri M, et al. Klinefelter's syndrome (47, XXY) in male systemic lupus erythematosus patients: support for the notion of a gene-dose effect from the X chromosome. Arthritis Rheum. 2008;58:2511–7.
14. Somers E, Marder W, Christman G, Ognenovski V, McCune W. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis Rheum. 2005;52:2761–7.
15. Masala A, Faedda R, Alagna S, Satta A, Chiarelli G, Rovasio P, et al. Use of testosterone to prevent cyclophosphamide-induced azoospermia. Ann Intern Med. 1997;126(4):292–5.

Rheumatoid Arthritis (RA)

16. Gomes V, Mesquita A, Capela C. Autoimmune diseases and pregnancy: analysis of a series of cases. BMC Res Notes. 2015;8:216.
17. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun. 2009;33(3–4):197–207.
18. Perricone C, de Carolis C, Perricone R. Pregnancy and autoimmunity: a common problem. Best Pract Res Clin Rheumatol. 2012;26(1):47–60.
19. Carp HJ, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. J Autoimmun. 2012;38(2–3):J266–74.
20. Borchers AT, Naguwa SM, Keen CL, Gershwin ME. The implications of autoimmunity and pregnancy. J Autoimmun. 2010;34(3):J287–99.
21. Ostanek L, Milchert M. Pregnancy associated with connective tissue disease. Ann Acad Med Stetin. 2006;52(Suppl 2):11–6.
22. Mecacci F, Pieralli A, Bianchi B, Paidas MJ. The impact of autoimmune disorders and adverse pregnancy outcome. Semin Perinatol. 2007;31(4):223–6.
23. Andreoli L, Fredi M, Nalli C, Reggia R, Lojacono A, Motta M, et al. Pregnancy implications for systemic lupus erythematosus and the antiphospholipid syndrome. J Autoimmun. 2012;38(2–3):J197–208.

24. Harward LE, Mitchell K, Pieper C, Copland S, Criscione-Schreiber LG, Clowse ME. The impact of cyclophosphamide on menstruation and pregnancy in women with rheumatologic disease. Lupus. 2013;22(1):81–6.
25. Medeiros PB, Febronio MV, Bonfa E, Borba EF, Takiuti AD, Silva CA. Menstrual and hormonal alterations in juvenile systemic lupus erythematosus. Lupus. 2009;18(1):38–43.
26. Blumenfeld Z, Shapiro D, Shteinberg M, Avivi I, Nahir M. Preservation of fertility and ovarian function and minimizing gonadotoxicity in young women with systemic lupus erythematosus treated by chemotherapy. Lupus. 2000;9(6):401–5.
27. Huong DL, Amoura Z, Duhaut P, Sbai A, Costedoat N, Wechsler B, et al. Risk of ovarian failure and fertility after intravenous cyclophosphamide. A study in 84 patients. J Rheumatol. 2002;29(12):2571–6.
28. Park MC, Park YB, Jung SY, Chung IH, Choi KH, Lee SK. Risk of ovarian failure and pregnancy outcome in patients with lupus nephritis treated with intravenous cyclophosphamide pulse therapy. Lupus. 2004;13(8):569–74.
29. McDermott EM, Powell RJ. Incidence of ovarian failure in systemic lupus erythematosus after treatment with pulse cyclophosphamide. Ann Rheum Dis. 1996;55(4):224–9.
30. Brunner HI, Bishnoi A, Barron AC, Houk LJ, Ware A, Farhey Y, et al. Disease outcomes and ovarian function of childhood-onset systemic lupus erythematosus. Lupus. 2006;15(4):198–206.
31. Riskalla MM, Somers EC, Fatica RA, McCune WJ. Tolerability of mycophenolate mofetil in patients with systemic lupus erythematosus. J Rheumatol. 2003;30(7):1508–12.
32. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005;353(21):2219–28.
33. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD. Garrido Ed Ede R, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002;46(8):2121–31.
34. Marder W, Fisseha S, Ganser MA, Somers EC. Ovarian Damage During chemotherapy in Autoimmune Diseases: Broad Health Implications beyond Fertility. Clin Med Insights Reprod Health. 2012;2012(6):9–18.
35. Henes M, Froeschlin J, Taran FA, Brucker S, Rall KK, Xenitidis T, et al. Ovarian reserve alterations in premenopausal women with chronic inflammatory rheumatic diseases: impact of rheumatoid arthritis, Behcet's disease and spondyloarthritis on anti-Mullerian hormone levels. Rheumatology. 2015;54(9):1709–12.
36. Ostensen M, Andreoli L, Brucato A, Cetin I, Chambers C, Clowse ME, et al. State of the art: Reproduction and pregnancy in rheumatic diseases. Autoimmun Rev. 2015;14(5):376–86.
37. Marder W, McCune WJ, Wang L, Wing JJ, Fisseha S, McConnell DS, et al. Adjunctive GnRH-a treatment attenuates depletion of ovarian reserve associated with cyclophosphamide therapy in premenopausal SLE patients. Gynecol Endocrinol (The Official Journal of the International Society of Gynecological Endocrinology). 2012;28(8):624–7.
38. Blumenfeld Z, Mischari O, Schultz N, Boulman N, Balbir-Gurman A. Gonadotropin releasing hormone agonists may minimize cyclophosphamide associated gonadotoxicity in SLE and autoimmune diseases. Semin Arthritis Rheum. 2011;41(3):346–52.
39. Blumenfeld Z, Patel B, Leiba R, Zuckerman T. Gonadotropin-releasing hormone agonist may minimize premature ovarian failure in young women undergoing autologous stem cell transplantation. Fertil Steril. 2012;98(5):1266–70.e1.
40. Clowse ME, Behera MA, Anders CK, Copland S, Coffman CJ, Leppert PC, et al. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. J Womens Health (Larchmt). 2009;18(3):311–9.
41. Blumenfeld Z, von Wolff M. GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy. Hum Reprod Update. 2008;14(6):543–52.
42. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis Rheum. 2005;52(9):2761–7.

43. Ince-Askan H, Dolhain RJ. Pregnancy and rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2015;29(4–5):580–96.
44. Smolen JS, Kurt R. Rheumatoid arthritis. The autoimmune diseases. Amsterdam: Elsevier/Academic Press; 2014. p. 511–23.
45. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res. 2002;4(Suppl 3):S265–72.
46. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United State. Part I. Arthritis Rheum. 2008;58(1):15–25.
47. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis Care Res. 2013;65(6):870–8.
48. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum. 1996;39(5):732–5.
49. Symmons DP, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DG, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfol, England. Arthritis Rheum. 1997;40(11):1955–61.
50. Mattey DL, Dawes PT, Clarke S, Fisher J, Brownfield A, Thomson W, et al. Relationship among the HLA-DRB1 shared epitope, smoking, and rheumatoid factor production in rheumatoid arthritis. Arthritis Rheum. 2002;47(4):403–7.
51. Klareskog L, Malmstrom V, Lundberg K, Padyukov L, Alfredsson L. Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis. Semin Immunol. 2011;23(2):92–8.
52. Yoshitomi H, Sakaguchi N, Kobayashi K, Brown GD, Tagami T, Sakihama T, et al. A role for fungal {beta}-glucans and their receptor Dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice. J Exp Med. 2005;201(6):949–60.
53. Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, Umesaki Y, et al. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity. 2010;32(6):815–27.
54. Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, et al. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. Br J Rheumatol. 1993;32(10):903–7.
55. Seldin MF, Amos CI, Ward R, Gregersen PK. The genetics revolution and the assault on rheumatoid arthritis. Arthritis Rheum. 1999;42(6):1071–9.
56. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham 3rd CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.
57. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995;38(1):38–43.
58. De Rycke L, Verhelst X, Kruithof E, Van den Bosch F, Hoffman IE, Veys EM, et al. Rheumatoid factor, but not anti-cyclic citrullinated peptide antibodies, is modulated by infliximab treatment in rheumatoid arthritis. Ann Rheum Dis. 2005;64(2):299–302.
59. Brouwer J, Hazes JM, Laven JS, Dolhain RJ. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis. 2015;74(10):1836–41.
60. Van Sinderen M, Menkhorst E, Winship A, Cuman C, Dimitriadis E. Preimplantation human blastocyst-endometrial interactions: the role of inflammatory mediators. Am J Reprod Immunol (New York, NY : 1989). 2013;69(5):427–40.
61. Micu MC, Micu R, Ostensen M. Luteinized unruptured follicle syndrome increased by inactive disease and selective cyclooxygenase 2 inhibitors in women with inflammatory arthropathies. Arthritis Care Res. 2011;63(9):1334–8.
62. Mendonca LL, Khamashta MA, Nelson-Piercy C, Hunt BJ, Hughes GR. Non-steroidal anti-inflammatory drugs as a possible cause for reversible infertility. Rheumatology. 2000;39(8):880–2.

63. de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum. 2008;59(9):1241–8.
64. Saketos M, Sharma N, Santoro NF. Suppression of the hypothalamic-pituitary-ovarian axis in normal women by glucocorticoids. Biol Reprod. 1993;49(6):1270–6.
65. Sakakura M, Takebe K, Nakagawa S. Inhibition of luteinizing hormone secretion induced by synthetic LRH by long-term treatment with glucocorticoids in human subjects. J Clin Endocrinol Metab. 1975;40(5):774–9.
66. Gordon D, Beastall GH, Thomson JA, Sturrock RD. Androgenic status and sexual function in males with rheumatoid arthritis and ankylosing spondylitis. Q J Med. 1986;60(231):671–9.
67. Hiwarkar P, Stasi R, Sutherland G, Shannon M. Deep vein and intracardiac thrombosis during the post-partum period in Behcet's disease. Int J Hematol. 2010;91(4):679–86.
68. Tolosa-Vilella C, Capela CA, Monteagudo-Jimenez M, Mari-Alfonso B. Infliximab for life-threatening pulmonary artery aneurysms in Behcet's disease. A case report. Clin Exp Rheumatol. 2011;29(4 Suppl 67):S94–5.
69. Busnelli A, Paffoni A, Fedele L, Somigliana E. The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis. Hum Reprod Update. 2016;22(6):775–90.
70. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ (Clinical research ed). 2011;342:d2616.
71. McGrogan A, Seaman HE, Wright JW, de Vries CS. The incidence of autoimmune thyroid disease: a systematic review of the literature. Clin Endocrinol (Oxf). 2008;69(5):687–96.
72. Vissenberg R, van Dijk MM, Fliers E, van der Post JA, van Wely M, Bloemenkamp KW, et al. Effect of levothyroxine on live birth rate in euthyroid women with recurrent miscarriage and TPO antibodies (T4-LIFE study). Contemp Clin Trials. 2015;44:134–8.
73. Abalovich M, Mitelberg L, Allami C, Gutierrez S, Alcaraz G, Otero P, et al. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. Gynecol Endocrinol (The Official Journal of the International Society of Gynecological Endocrinology). 2007;23(5):279–83.
74. van den Boogaard NM, van den Boogaard E, Bokslag A, van Zwieten MC, Hompes PG, Bhattacharya S, et al. Patients' and professionals' barriers and facilitators of tailored expectant management in subfertile couples with a good prognosis of a natural conception. Hum Reprod. 2011;26(8):2122–8.
75. Unuane D, Velkeniers B, Anckaert E, Schiettecatte J, Tournaye H, Haentjens P, et al. Thyroglobulin autoantibodies: is there any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment? Thyroid (Official Journal of the American Thyroid Association). 2013;23(8):1022–8.
76. Baker Jr WF, Bick RL. The clinical spectrum of antiphospholipid syndrome. Hematol Oncol Clin North Am. 2008;22(1):33–52. v-vi
77. Bellver J, Pellicer A. Ovarian stimulation for ovulation induction and in vitro fertilization in patients with systemic lupus erythematosus and antiphospholipid syndrome. Fertil Steril. 2009;92(6):1803–10.
78. Fritz MA, Speroff L. Recurrent Early Pregnancy Loss 0030. In: Fritz MA, Speroff L, editors. Clinical Gynecologic Endocrinology and Infertility. 8th ed. Philadelphia: Wolters Kluwer; 2011.
79. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramon E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis. 2015;74(6):1011–8.
80. Gezer S. Antiphospholipid syndrome. Dis Mon. 2003;49(12):696–741.
81. Faussett MB, Branch DW. Autoimmunity and pregnancy loss. Semin Reprod Med. 2000;18(4):379–92.
82. Lockwood CJ, Romero R, Feinberg RF, Clyne LP, Coster B, Hobbins JC. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin antibodies in a general obstetric population. Am J Obstet Gynecol. 1989;161(2):369–73.

83. Pattison NS, Chamley LW, McKay EJ, Liggins GC, Butler WS. Antiphospholipid antibodies in pregnancy: prevalence and clinical associations. Br J Obstet Gynaecol. 1993;100(10):909–13.
84. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol. 1992;80(4):614–20.
85. Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial comparing prednisone with low-dose heparin treatment. Am J Obstet Gynecol. 1992;166(5):1318–23.
86. Lima F, Khamashta MA, Buchanan NM, Kerslake S, Hunt BJ, Hughes GR. A study of sixty pregnancies in patients with the antiphospholipid syndrome. Clin Exp Rheumatol. 1996;14(2):131–6.
87. Branch DW, Dudley DJ, Mitchell MD, Creighton KA, Abbott TM, Hammond EH, et al. Immunoglobulin G fractions from patients with antiphospholipid antibodies cause fetal death in BALB/c mice: a model for autoimmune fetal loss. Am J Obstet Gynecol. 1990;163(1 Pt 1):210–6.
88. Blank M, Cohen J, Toder V, Shoenfeld Y. Induction of anti-phospholipid syndrome in naive mice with mouse lupus monoclonal and human polyclonal anti-cardiolipin antibodies. Proc Natl Acad Sci U S A. 1991;88(8):3069–73.
89. Chamley LW, Pattison NS, McKay EJ. The effect of human anticardiolipin antibodies on murine pregnancy. J Reprod Immunol. 1994;27(2):123–34.
90. Chighizola CB, de Jesus GR, Branch DW. The hidden world of anti-phospholipid antibodies and female infertility: A literature appraisal. Autoimmun Rev. 2016;15(6):493–500.
91. Triplett DA. Antiphospholipid antibodies. Arch Pathol Lab Med. 2002;126(11):1424–9.
92. Silver RM, Porter TF, van Leeuween I, Jeng G, Scott JR, Branch DW. Anticardiolipin antibodies: clinical consequences of "low titers". Obstet Gynecol. 1996;87(4):494–500.
93. Branch DW, Silver R, Pierangeli S, van Leeuwen I, Harris EN. Antiphospholipid antibodies other than lupus anticoagulant and anticardiolipin antibodies in women with recurrent pregnancy loss, fertile controls, and antiphospholipid syndrome. Obstet Gynecol. 1997;89(4):549–55.
94. Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol. 1996;174(5):1584–9.
95. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ (Clinical research ed). 1997;314(7076):253–7.
96. Backos M, Rai R, Baxter N, Chilcott IT, Cohen H, Regan L. Pregnancy complications in women with recurrent miscarriage associated with antiphospholipid antibodies treated with low dose aspirin and heparin. Br J Obstet Gynaecol. 1999;106(2):102–7.
97. Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev. 2005;2:Cd002859.
98. Ziakas PD, Pavlou M, Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. Obstet Gynecol. 2010;115(6):1256–62.
99. Bar J, Cohen-Sacher B, Hod M, Blickstein D, Lahav J, Merlob P. Low-molecular-weight heparin for thrombophilia in pregnant women. Int J Gynaecol Obstet (The Official Organ of the International Federation of Gynaecology and Obstetrics). 2000;69(3):209–13.
100. Younis JS, Ohel G, Brenner B, Haddad S, Lanir N, Ben-Ami M. The effect of thrombophylaxis on pregnancy outcome in patients with recurrent pregnancy loss associated with factor V Leiden mutation. BJOG. 2000;107(3):415–9.
101. Brenner B, Hoffman R, Blumenfeld Z, Weiner Z, Younis JS. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. Thromb Haemost. 2000;83(5):693–7.

102. Chighizola CB, de Jesus GR. Antiphospholipid antibodies and infertility. Lupus. 2014;23(12):1232–8.
103. A rational basis for antiphospholipid antibody testing and selective immunotherapy in assisted reproduction: a rebuttal to the American Society for Reproductive Medicine Practice opinion. American Society for Reproductive Immunology Antiphospholipid Antibody Committee. Fertil Steril. 2000;74(4):631–4.
104. Carp HJ, Meroni PL, Shoenfeld Y. Autoantibodies as predictors of pregnancy complications. Rheumatology. 2008;47(Suppl 3):iii6–8.
105. Humaidan P, Polyzos NP, Alsbjerg B, Erb K, Mikkelsen AL, Elbaek HO, et al. GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. Hum Reprod. 2013;28(9):2511–21.
106. Henriksson P, Westerlund E, Wallen H, Brandt L, Hovatta O, Ekbom A. Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study. BMJ (Clinical research ed). 2013;346:e8632.
107. Guballa N, Sammaritano L, Schwartzman S, Buyon J, Lockshin MD. Ovulation induction and in vitro fertilization in systemic lupus erythematosus and antiphospholipid syndrome. Arthritis Rheum. 2000;43(3):550–6.
108. Ferro F, Vagelli R, Bruni C, Cafaro G, Marcucci E, Bartoloni E, et al. One year in review 2016: Sjogren's syndrome. Clin Exp Rheumatol. 2016;34(2):161–71.
109. Ramos-Casals M, Brito-Zeron P, Kostov B, Siso-Almirall A, Bosch X, Buss D, et al. Google-driven search for big data in autoimmune geoepidemiology: analysis of 394,827 patients with systemic autoimmune diseases. Autoimmun Rev. 2015;14(8):670–9.
110. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, et al. Epidemiology of primary Sjogren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74(11):1983–9.
111. Mavragani CP, Fragoulis GE, Haralampos MM. Sjögren's Syndrome. The Autoimmune Diseases. 2014. p. 495–510.
112. Moutsopoulos HM. Sjogren's syndrome or autoimmune epithelitis? Clin Rev Allergy Immunol. 2007;32(3):199–200.
113. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjogren's syndrome. Arthritis Rheum. 2002;46(3):741–7.
114. Voulgarelis M, Ziakas PD, Papageorgiou A, Baimpa E, Tzioufas AG, Moutsopoulos HM. Prognosis and outcome of non-Hodgkin lymphoma in primary Sjogren syndrome. Medicine. 2012;91(1):1–9.
115. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjogren syndrome. Arch Intern Med. 2004;164(12):1275–84.
116. Garcia-Carrasco M, Siso A, Ramos-Casals M, Rosas J, de la Red G, Gil V, et al. Raynaud's phenomenon in primary Sjogren's syndrome. Prevalence and clinical characteristics in a series of 320 patients. J Rheumatol. 2002;29(4):726–30.

Chapter 9
Autoimmune Diseases: Myasthenia Gravis and Multiple Sclerosis

Myasthenia Gravis (MG)

Definition

Chronic autoimmune disease of the neuromuscular junction [1]. It is an autoantibody-mediated disease. In most patients, IgG1-dominant antibodies to nicotinic acetylcholine receptors (AChR) cause fatigable weakness of skeletal muscles with an ocular onset in up to 85% [2, 3].

Physiopathology

Autoantibodies against the muscle nicotinic AChR are present in up to 80% of patients with MG [4, 5] (AChR) within the muscle end plate zone of the neuromuscular junction (NMJ). Recently described muscle-specific kinase (MuSK) antibody-mediated (MG) (MuSK-MG) has features clinically distinct from Ach-R MG, as well as a different pattern of response to treatment and a unique immunopathogenesis [4].

Incidence

The incidence and prevalence of MG are increasing, particularly in older individuals. However, MG remains a rare disease with a prevalence rate (PR) of 77.7 cases per million of the population. Prevalence has been rising since the middle of the last century, with improved recognition and diagnosis, medical and intensive care advances, and patient longevity [2].

Under the age of 40, myasthenia is significantly more common in women [3].

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_9

Diagnosis

Diagnostic tests:

1. Serum anti-acetylcholine receptor (ACh-R) antibody testing: first-line investigation for non-urgent patients.
2. Thyroid function.
3. Serum anti-muscle-specific kinase (MuSK) antibody testing for all patients negative for ACh-R antibodies.
4. Neurophysiology test: may help to establish the diagnosis in seronegative patients with suspected myasthenia gravis.
5. MR scan of brain: patients with negative serology and neurophysiology and symptoms compatible with ocular myasthenia may have structural brain disease.
6. Thymus scanning: All patients with suspected myasthenia, irrespective of distribution (ocular/generalized) or serology (seropositive/negative), should undergo thymus imaging (CT or MRI).
7. Referral to a myasthenia specialist: if tests are negative and myasthenia is still suspected or if a congenital myasthenia syndrome is suspected. (Congenital may mimic seronegative autoimmune myasthenia.)
8. Edrophonium/tensilon test. if there is diagnostic doubt, refer to a myasthenia gravis specialist [1].

Confirmation of diagnosis and subtype:

- ACh-R/MuSK seropositive/seronegative
- Thymoma/no thymoma
- Ocular/generalized

When myasthenia is suspected but tests are negative, the physician must consider a muscle disorder or refer to a myasthenia expert for management [1].

Diagnosis is made through recognition of:

- Clinical features of fatigable, painless muscle weakness
- Confirmatory serum autoantibody analysis
- Electromyographic evidence of disordered neuromuscular transmission

Clinical Presentation

Myasthenia gravis (MG) is a chronic autoimmune disorder of neuromuscular transmission characterized by varying degrees of weakness and easy fatigability of the skeletal muscles [5].

Clinical presentations of MuSK-MG also include a syndrome of fatigable, generalized weakness more closely resembling ACh-R MG (except for ocular symptoms), as well as a syndrome of severe facial and bulbar weakness with respiratory crisis [4].

Treatment

- Pyridostigmine and corticosteroids retain a central role in the management of GMG [2].
- Treatment of ocular MG.
- Pyridostigmine.
- If the serum ACh-R antibody is positive and the patient is aged under 45 years, thymectomy at presentation should be considered.
- If symptomatic despite pyridostigmine, prednisolone should be started.
- If symptoms relapse on prednisolone, immunosuppression with azathioprine should be considered.
- Other immunosuppressive agents as mycophenolate mofetil, methotrexate, cyclosporine, and rituximab.
- Patients should be managed in the hospital in case of significant bulbar symptoms, low vital capacity, respiratory symptoms, or progressive deterioration [1].

Effect on Fertility

Reduced fertility/reduced ovarian reserve in MG could be due to the effects of medications [3].

Multiple Sclerosis

Definition

Multiple sclerosis (MS) is an autoimmune condition affecting the central nervous system (CNS). The pathological hallmarks of MS are diffuse and focal areas of inflammation, demyelination, gliosis, and neuronal injury in the brain and spinal cord [6].

Epidemiology

MS is the most common nontraumatic cause of neurological disability in persons younger than 40 years. It mainly affects young people, with onset usually at the age of 20–40 years, and it occurs in a female-to-male ratio of 3–1 [6–8].

Clinical Course

Clinical course of the disease is highly variable:

- 85–90% of patients at disease onset have a *relapsing-remitting MS* (RRMS) course, characterized by clearly defined attacks of new or recurrent neurological symptoms and signs, followed by a full or partial recovery.
- In 10–15% of the cases, the disease is characterized by a disability progression from onset, with occasional plateaus and temporary improvements (*a primary progressive course*) [6].

Natural History

Approximately 50% of RRMS patients after 10 years and 90% after 25 years convert to secondary progressive MS (SPMS), characterized by disability progression with or without occasional relapses, minor remissions, and plateaus [6, 9, 10].

Treatment

Therapies can be classified as first-line and second-line (used in patients who do not respond satisfactorily to a first-line therapy or in patients with very active RRMS) treatments [6, 11, 12].

Therapies for RRMS include:

- Interferon (IFN)-β, (intramuscular or subcutaneous)
- Glatiramer acetate (GA)
- Natalizumab
- Fingolimod
- Mitoxantrone
- Newer agents: teriflunomide, alemtuzumab, and dimethyl fumarate.

Effect on Fertility

The female-to-male ratio has increased in recent decades [13], and this fact probably has to do with lifestyle habits:

- Smoking
- Sunlight exposure

- Vitamin D deficiency [14]

Epigenetic factors and gene–environment interactions [15]. Also, the times to diagnosis and to treatment have been significantly shortened [6, 16].

Sexual dysfunction:

- Usually underreported by patients [17, 18].
- Prevalence ranges from 30 to 70% of cases, depending on the clinical characteristics of study samples and on follow-up durations.

Women with MS most frequently report:

- Decreased libido (36–86% of cases).
- Difficulty in achieving orgasm (28–58%).
- Reduction in the tactile sensations from genital areas (43–62%).
- Dyspareunia (8–40%) [19].
- Symptoms of sexual dysfunction including vaginal sensory disturbances and lubrication, which are known to occur also in patients in early states of the disease.
- Psychosocial factors may influence the decision to have children.

Men most frequently report:

- Reduced libido (37–86%)
- Erectile dysfunction (34–80%)
- Reduction in tactile sensations (21–72%)
- Ejaculatory dysfunction (34–61%)
- Reduced orgasmic capacity (29–64%) [20]

In both sexes:

- Bladder and bowel disturbances may contribute to affect sexual activity, interfering with social relationships and with intimate behavior [20].

MS does not appear to impair fertility in women with MS [21]. It has to be noted that assisted reproductive techniques using gonadotropin-releasing hormone (GnRH) agonists and gonadotropins are probably related to the occurrence of MRI activity and an increase in the relapse rate following in vitro fertilization [22]. Indeed, GnRH affects immune cell proliferation; cytokine, chemokine, and endothelial growth factor production; and estrogen levels.

Interferon and Glatiramer Acetate:
There is no evidence that these drugs impair women fertility [23].

IFN and GA do not seem to alter the sperm count and are usually not withdrawn if a man wants to become a father [24].

Formal reports on the effects of these drugs on male fertility are lacking [6].

Natalizumab
There are no studies on the effects of natalizumab on human fertility [6].

Fingolimod
No evidence of effect on male or female fertility [6]

Mitoxantrone and Cyclophosphamide:
Treatment with mitoxantrone caused long-lasting amenorrhea linked to a reduction of the ovarian reserve in up to 17.3% of women under 45 years of age in a large French series [25]. Administration of estroprogestinic therapy reduced the risk of amenorrhea [25].

In men, transient azoospermia was described after NOVP (mitoxantrone, vincristine, vinblastine, and prednisone) chemotherapy, with recovery after 3–4 months [26].

Cyclophosphamide
Cyclophosphamide has a toxic effect on ovarian follicles and finally reduces the ovarian reserve and the availability of female gametes [27] particularly in women older than 31 years, as well as in long-term therapy.

In male patients receiving cyclophosphamide, severe gonadal dysfunction, with transient or permanent azoospermia, is found in 50–90% [28]. Germinal cells are vulnerable because of their high mitotic activity; the effect appears to be age dependent and dose dependent [6].

The immunosuppressants mitoxantrone and cyclophosphamide are associated with reduced fertility and reproductive toxicity [6].

Very Few Studies Have Assessed Fertility in Patients with MS
Women with MS are more likely to be childless than the general population, but it is not clear whether this owes to decreased fertility or—what we consider to be more likely—to a choice of avoiding pregnancy.

Women with MS can face difficulties in becoming pregnant and might wish to undergo assisted reproduction techniques (ARTs) [29].

ART seems to increase the risk of relapse. The findings are clearly not sufficient to contraindicate ART in women with MS, but neurologists should inform their patients of this possibility [29].

Many people with MS are young women of childbearing age, for whom pregnancy is often a major concern [30].

There have been some reports suggesting that fertility, defined as the number of children that are born to women with MS, is reduced [30].

For people with a medical condition, fertility could be impaired either by:

- Health issues (including the effect of therapy) leading to reduced ability to conceive.
- Social issues such as reduced opportunity to find a partner or a decision to avoid pregnancy because of disability. In MS, it seems probable that social issues are important and could lead women with MS to have fewer pregnancies even if their ability to conceive is normal.

Some reports suggest that women with MS may have reduced ability to conceive [30]. One study, using transvaginal ultrasound to evaluate ovarian volume, follicle count, and ovarian artery Doppler found low ovarian reserve in MS patients [30]. Thone et al. show that AMH levels were lower in young women with relapsing-remitting MS compared with controls. While this is a small study, it provides evidence that women with MS may have reduced ovarian reserve and hence reduced

fertility [30]. Thone et al. found that levels of AMH were lower in women who were not already on medications.

The reduced ovarian reserve could be due to a neuroendocrine effect of MS [30].

Present results about the prevalence and cause of infertility in MS are scarce and conflicting, show gender differences, and thus call for further research [30].

There are few studies of male fertility in MS, and these focus mainly on sexual dysfunction, [31] although one study found that males with MS had reduced semen quality and hypogonadotropic hypogonadism.

Nevertheless, women with multiple sclerosis are more common childless and, according to a finish dataset, undergo more common assisted reproductive techniques (ART) [21].

Several factors might contribute to a slightly impaired fertility in women with MS:

- Hormonal alteration, including higher levels on prolactin, LH, and FSH in combination with reduced estrogens, is described [32].
- Concomitant (autoimmune) thyroid disease (AIT) could interfere with fertility, although it is not evident if the prevalence of AIT is raised in MS patients [33].

Although the true incidence of infertility in MS patients is not known, in Western countries, 10–20% of all couples suffer from infertility [34], and infertility and MS might just come coincidentally together [21].

References

Myasthenia Gravis (MG)

1. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: association of British Neurologists' management guidelines. Practical neurology. 2015;15(3):199–206.
2. Binks S, Vincent A, Palace J. Myasthenia gravis: a clinical-immunological update. J Neurol. 2016;263(4):826–34.
3. Norwood F, Dhanjal M, Hill M, James N, Jungbluth H, Kyle P, et al. Myasthenia in pregnancy: best practice guidelines from a U.K. multispecialty working group. J Neurol Neurosurg Psychiatry. 2014;85(5):538–43.
4. Hurst RL, Gooch CL. Muscle-Specific Receptor Tyrosine Kinase (MuSK) Myasthenia Gravis. Curr Neurol Neurosci Rep. 2016;16(7):61.
5. Wen JC, Liu TC, Chen YH, Chen SF, Lin HC, Tsai WC. No increased risk of adverse pregnancy outcomes for women with myasthenia gravis: a nationwide population-based study. Eur J Neurol. 2009;16(8):889–94.

Multiple Sclerosis

6. Amato MP, Portaccio E. Fertility, pregnancy and childbirth in patients with multiple sclerosis: impact of disease-modifying drugs. CNS Drugs. 2015;29(3):207–20.
7. Compston A, Coles A. Multiple sclerosis. Lancet (London, England). 2008;372(9648):1502–17.

8. Niedziela N, Adamczyk-Sowa M, Pierzchala K. Epidemiology and clinical record of multiple sclerosis in selected countries: a systematic review. Int J Neurosci. 2014;124(5):322–30.
9. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology. 1996;46(4):907–11.
10. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278–86.
11. Rieckmann P, Toyka KV, Bassetti C, Beer K, Beer S, Buettner U, et al. Escalating immunotherapy of multiple sclerosis--new aspects and practical application. J Neurol. 2004;251(11):1329–39.
12. Sorensen PS. New management algorithms in multiple sclerosis. Curr Opin Neurol. 2014;27(3):246–59.
13. Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol. 2006;5(11):932–6.
14. Sellner J, Kraus J, Awad A, Milo R, Hemmer B, Stuve O. The increasing incidence and prevalence of female multiple sclerosis--a critical analysis of potential environmental factors. Autoimmun Rev. 2011;10(8):495–502.
15. Chao MJ, Ramagopalan SV, Herrera BM, Orton SM, Handunnetthi L, Lincoln MR, et al. MHC transmission: insights into gender bias in MS susceptibility. Neurology. 2011;76(3):242–6.
16. Marrie RA, Cutter G, Tyry T, Hadjimichael O, Campagnolo D, Vollmer T. Changes in the ascertainment of multiple sclerosis. Neurology. 2005;65(7):1066–70.
17. Cavalla P, Rovei V, Masera S, Vercellino M, Massobrio M, Mutani R, et al. Fertility in patients with multiple sclerosis: current knowledge and future perspectives. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2006;27(4):231–9.
18. Nortvedt MW, Riise T, Myhr KM, Landtblom AM, Bakke A, Nyland HI. Reduced quality of life among multiple sclerosis patients with sexual disturbance and bladder dysfunction. Mult Scler (Houndmills, Basingstoke, England). 2001;7(4):231–5.
19. Borello-France D, Leng W, O'Leary M, Xavier M, Erickson J, Chancellor MB, et al. Bladder and sexual function among women with multiple sclerosis. Mult Scler (Houndmills, Basingstoke, England). 2004;10(4):455–61.
20. Zorzon M, Zivadinov R, Bosco A, Bragadin LM, Moretti R, Bonfigli L, et al. Sexual dysfunction in multiple sclerosis: a case-control study. I. Frequency and comparison of groups. Mult Scler (Houndmills, Basingstoke, England). 1999;5(6):418–27.
21. Hellwig K, Correale J. Artificial reproductive techniques in multiple sclerosis. Clin Immunol. 2013;149(2):219–24.
22. Hellwig K, Schimrigk S, Beste C, Muller T, Gold R. Increase in relapse rate during assisted reproduction technique in patients with multiple sclerosis. Eur Neurol. 2009;61(2):65–8.
23. Sandberg-Wollheim M, Frank D, Goodwin TM, Giesser B, Lopez-Bresnahan M, Stam-Moraga M, et al. Pregnancy outcomes during treatment with interferon beta-1a in patients with multiple sclerosis. Neurology. 2005;65(6):802–6.
24. Lu E, Zhu F, Zhao Y, van der Kop M, Sadovnick AD, Synnes A, et al. Birth outcomes of pregnancies fathered by men with multiple sclerosis. Mult scler (Houndmills, Basingstoke, England). 2014;20(9):1260–4.
25. Cocco E, Sardu C, Gallo P, Capra R, Amato MP, Trojano M, et al. Frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis: the FEMIMS study. Mult Scler (Houndmills, Basingstoke, England). 2008;14(9):1225–33.
26. Meistrich ML, Wilson G, Mathur K, Fuller LM, Rodriguez MA, McLaughlin P, et al. Rapid recovery of spermatogenesis after mitoxantrone, vincristine, vinblastine, and prednisone chemotherapy for Hodgkin's disease. J Clin Oncol Off J Am Soc Clin Oncol. 1997;15(12):3488–95.
27. Awad A, Stuve O. Cyclophosphamide in multiple sclerosis: scientific rationale, history and novel treatment paradigms. Ther Adv Neurol Disord. 2009;2(6):50–61.
28. Watson AR, Rance CP, Bain J. Long term effects of cyclophosphamide on testicular function. Br Med J (Clin Res Ed). 1985;291(6507):1457–60.

29. Vukusic S, Marignier R. Multiple sclerosis and pregnancy in the treatment era. Nat Rev Neurol. 2015;11(5):280–9.
30. McCombe PA, Stenager E. Female infertility and multiple sclerosis: is this an issue? Multiple sclerosis (Houndmills, Basingstoke, England). 2015;21(1):5–7.
31. Voskuhl RR, Gold SM. Sex-related factors in multiple sclerosis susceptibility and progression. Nat Rev Neurol. 2012;8(5):255–63.
32. Grinsted L, Heltberg A, Hagen C, Djursing H. Serum sex hormone and gonadotropin concentrations in premenopausal women with multiple sclerosis. J Intern Med. 1989;226(4):241–4.
33. Marrie RA, Yu BN, Leung S, Elliott L, Warren S, Wolfson C, et al. The incidence and prevalence of thyroid disease do not differ in the multiple sclerosis and general populations: a validation study using administrative data. Neuroepidemiology. 2012;39(2):135–42.
34. Gnoth C, Godehardt E, Frank-Herrmann P, Friol K, Tigges J, Freundl G. Definition and prevalence of subfertility and infertility. Hum Reprod (Oxford, England). 2005;20(5):1144–7.

Chapter 10
Chronic Kidney Disease

Definition

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure, morphology, imaging, or function or by a glomerular filtration rate (GFR) <60 mL/min, present for at least 3 months, with implications for health [1–3].

National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) working group decided to use a developed and an operational definition of CKD.

Kidney damage could be either:

1. Pathological abnormalities of the kidney such as the presence of polycystic kidney disease
2. The presence of markers of kidney damage such as proteinuria
3. GFR less than 60 ml/min/1.73 m^2 without any other evidence of kidney damage

Changes in GFR are not an "early" marker of disease, as it starts decreasing when >50% of the renal parenchyma is damaged; hence, it is important to identify CKD in stage 1, when kidney function is normal and CKD is revealed by proteinuria, hematuria, electrolyte derangements, tubulointerstitial diseases, single kidney (including kidney donation), or even "simple" kidney scars due to previous acute pyelonephritis [2].

Risk Factors for Kidney Failure

Clinical Factors

- Diabetes
- Hypertension

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_10

- Autoimmune diseases
- Systemic infections
- Urinary tract infections
- Urinary stones
- Lower urinary tract obstruction
- Family history of chronic kidney diseases
- Recovery from acute kidney failure
- Reduction in kidney mass
- Exposure to certain drugs
- Low birth weight

Identification of CKD in a middle-aged individual is a signal for cardiovascular disease risk, and additional steps can be taken to reduce the rates of myocardial infarction, stroke, heart failure, and cardiovascular death. It all starts with screening and detection of a silent disease, which give years of opportunity for discovery and modification of its natural history [3].

Incidence

CKD is a global public health problem with a rising prevalence. There is no accepted definition of CKD incidence; it is difficult to ascertain as it requires establishment of a cohort with normal kidney function at baseline with serial measurements of kidney function over a long period [4]. On the basis of these broad definitions, the prevalence of CKD reaches 3% in women in childbearing age, a significant difference as compared to previous definitions, which were based upon high creatinine levels that probably identified <10% of cases [2, 5].

Physiopathology

Renal parenchymal disease is the result of a variety of acute and chronic insults that can lead to nephron loss followed by adaptive hyperfiltration in the remaining nephrons. This adaptive hyperfiltration results in long-term glomerular damage leading to proteinuria and progressive loss of renal function [4].

Clinical Manifestations

The initial decline of renal function is asymptomatic, and clinical manifestations of kidney failure occur late in the course of the disease. The loss of renal function, however, is variable and can be relentless even despite optimal medical therapy [4].

Stages of CKD

K/DOQI classification:
Stage 1 Kidney damage with normal or increased GFR ≥90
Stage 2 Kidney damage with mild decrease in GFR 60–89
Stage 3 Moderate decrease in GFR 30–59

3a (GFR 45–59)
3b (GFR 30–44)

Stage 4 Severe decrease in GFR 15–29
Stage 5 Kidney failure ≤ 14 (1–4)
Markers of kidney damage (need the presence of one or more):

- Albuminuria (AER ≥30 mg/24 h; ACR ≥ 30 mg/g (≥3 mg/mmol)
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation [1]

Epidemiology of Chronic Kidney Disease

- Older age
- US ethnic minority status: African American, American Indian, Hispanic, Asian, or Pacific Islander
- Exposure to certain chemical and environmental conditions
- Low income/education [1]

Etiology of Chronic Kidney Disease

CKD can result from any underlying kidney disease that results from either acute kidney injury or a slowly progressive kidney disease. End-stage renal disease (ESRD) patients are disease "survivors" who initiate renal replacement therapy (dialysis and kidney transplantation) [1].

Risk Factors for ESRD

- Male gender

- Older age
- Proteinuria
- DM
- Lower educational attainment
- African American race
- Higher blood pressure
- Body mass index
- Serum creatinine level [4]

Evaluation of Cause

To determine causes of kidney disease, clinical context, including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis, should be evaluated [1].

Treatment

Patients with progressive CKD need to be managed in a multidisciplinary care setting.

The team should include dietary counseling, education, transplant options, vascular access surgery, and ethical, psychological, and social care [1].

- Dialysis

Dialysis should be initiated when one or more of the following are present:

- Symptoms or signs attributable to kidney failure (serositis, acid base or electrolyte abnormalities, pruritus)
- Inability to control volume status or blood pressure
- Progressive deterioration in nutritional status refractory to dietary intervention
- Cognitive impairment [1]

These symptoms often but not invariably occur in the GFR range between 5 and 10 ml/min/1.73 m2.

- Cyclophosphamide

It is the immunosuppressant drug of choice for the treatment of patients with severe systemic lupus erythematosus (SLE), antineutrophil cytoplasmic antibody-associated vasculitides, and glomerulonephritis and is widely used for the treatment of patients with various immune-mediated rheumatic, renal, neurological, and hematologic diseases or their complications [1].

Fertility in Women with ESRD

CKD can affect women during their childbearing years. As kidney function declines, fertility is reduced due to complex physiologic changes [6–9].

Although the precise mechanisms that contribute to infertility in women with ESRD are not fully understood, considerable hormonal changes and issues with sexual function occur as a young woman's kidneys fail.

Infertility in men and women with CKD is common and is caused by abnormalities in multiple areas of reproductive physiology; sexual dysfunction including impotence, loss of libido, impaired spermatogenesis, anovulation, and derangements in the hormonal control of fertility are all involved.

Chronic renal failure in women is frequently accompanied by endocrine disturbances. Patients have alterations in their hypothalamic–pituitary–ovarian axis and increase of follicle-stimulating hormone,and luteinizing hormone levels [10, 11] which lead to menstrual irregularities, anovulation, and decreased fertility [11–13].

Most women with ESRD experience amenorrhea or oligomenorrhea due to decreased levels of estrogen and progesterone which can result in significant changes to uterine morphology, including atrophy [14]. Even in women who continue to menstruate, anovulatory cycles are typical due to aberrant follicle-stimulating hormone levels and the absence of the cyclical surge of luteinizing hormone necessary for ovulation. Inhibition of the estradiol-stimulated LH surge seems to be responsible for anovulatory cycles. Elevated luteinizing hormone (LH) levels are characteristic of men and women on dialysis. In men on dialysis, it is believed that impaired spermatogenesis and low testosterone levels stimulate LH. High prolactin levels are also common in men and women on dialysis and may be another hormonal contributor to infertility. The increased prolactin is due to a decreased response to dopamine inhibition and compromised prolactin metabolic clearance which is reversed by transplantation [14]. Studies reported 3.9% of POI which is higher than the prevalence of 1% in the general population, and pregnancy incidence in women on HD and peritoneal dialysis (PD) has been documented to be very low [14].

Innovations in HD, though, are reflected in increased pregnancy rates over time and have been described in data from the United States and other countries, patients achieve significantly higher clearance rates with intensive nocturnal HD, conception rates are higher than previously reported cohorts, and patients treated by slow nocturnal hemodialysis are now more likely to conceive. Current clinical data show increased conception rates and increased successful pregnancy outcomes with nocturnal dialysis [15, 16]. This is likely due to normalization of the hypothalamic–pituitary–gonadal axis, as evidenced by the return of regular menstrual cycles in more intensively dialyzed young women [17]. However, management of CKD with dialytic therapy increases survival rate, but infertility usually persists [16].

Kidney transplantation (KT) has become the best choice for young patients with CKD because it increases reproductive function in those women who wish for motherhood [18]. Most studies of fertility in those with kidney disease focus on

dialysis patients. Successful kidney transplantation restores fertility and the normal hormonal milieu necessary for reproduction [7].

Pregnancy may promote a decline in precarious native or transplant kidney function and precipitate the need for dialysis therapy [6].

Although preeclampsia, prematurity, and small-for-gestational-age infants are more common in women with earlier stages of CKD than in the healthy population, 74% of pregnancies in women with a creatinine level of 1.4 mg/dL result in live births. Deshpande's meta-analysis reported a live birth rate in transplant patients of 73.5%. With increasing experience with pregnancy, some nephrologists advocate for less restrictive recommendations regarding pregnancy in CKD. Birth rate in transplant recipients appears to be higher than that found in the US general population [10, 15].

American Society of Transplantation recommends that pregnancy can be attempted at least 1 year after renal transplantation, if the renal function is good and stable, and in the absence of uncontrollable hypertension. When authorized by the nephrologist, pregnancy must benefit from a multidisciplinary management and close obstetric monitoring to decide the optimal timing of delivery [11].

Maternal Complications

If pregnancy occurs, there may be significant maternal and fetal morbidity or mortality and adverse outcomes. In women receiving dialysis or with a kidney transplant, live [6] birth rates are improving, leading to more permissive attitudes toward pregnancy, but these pregnancies remain high risk, with increased fetal loss and prematurity [10].

Abnormal Smear Test

The improved life expectancy of women on dialysis, and then after kidney transplantation, is due in large part to advances in long-term immunosuppressive treatment. This may, however, increase the incidence of diseases associated with human papillomavirus infection, such as condylomas, cervical intraepithelial neoplasia, and cervical cancer [19, 20] . Consequently, this population must have close follow-up to identify and treat gynecologic issues [11]. Systematic annual cervical screening should therefore be advised [11].

Contraception

After kidney transplantation, the hypothalamic–pituitary–ovarian axis function rapidly improves in many women, and fertility is often restored rapidly [21, 22]. Nevertheless, the potential for pregnancy is much greater than in

women with kidney failure, making contraceptive use essential [10]. The combined contraceptive pill is believed to be relatively contraindicated because of the increased risk of cardiovascular disease [23]. In the same way, practitioners fear a decreased effectiveness of the intrauterine device (IUD) due to immunosuppressive agents among transplanted patients and an increased risk of infection hypotheses which are based on only a couple of case reports [11]. Risk Evaluation and Mitigation Strategy program recommends that acceptable contraception includes IUD alone, tubal ligation, partner vasectomy, or combining one hormone and one barrier method or combining two barrier methods [10, 17].

Compared with the general public, the pregnancy rates are lower in women with kidney transplants [10].

Few studies have described menstrual irregularities, amenorrhea and dysfunctional uterine bleeding in women on dialysis, which could be restored along with fertility after successful renal transplantation [11, 24, 25].

Cyclophosphamide

Gonadal failure after immunosuppressive therapy with cyclophosphamide is a common finding in medical practice, often leading to infertility in young patients [26].

Alterations in gonadal function are probably the most common long-term side effects of chemotherapy [26].

Testicular damage is drug specific and dose related [27]. Gonadal dysfunction after treatment may be temporary, but recovery is often unpredictable, and damage is permanent in a large proportion of patients; severe gonadal failure with transient or permanent azoospermia is found in 50–90% of men receiving cyclophosphamide [28]. The concern about fertility can have a critical role in the decision to refuse treatment with cyclophosphamide and other alkylating agents, such as chlorambucil [26].

However, the impact of this therapy on fertility is an important consideration for many patients [26]. Prepubertal patients who receive large doses of cyclophosphamide seem to recover their gonadal function better than adult's; normal pubertal development and normal spermatogenesis have been reported in many of these patients, suggesting that active germinal cells are more sensitive to cyclophosphamide because of their increased mitotic activity. These observations have led to many trials of suppression of gonadal function, with the aim toward inducing a prepuberty [26].

Testosterone administered to men receiving cyclophosphamide for various forms of glomerulonephritis may have a protective role in gonadal function [26]; FSH levels increased in men who received cyclophosphamide alone, suggesting a significant effect on testicular function, whereas they remained within the normal range in men who received testosterone therapy. LH levels were normal in all 15 patients, suggesting that Leydig cell function was not affected [26].

Although the ovary seems to be less vulnerable to the cytotoxic effects of chemotherapy or radiotherapy than the testis, ovarian failure (OF) is not uncommon after cytotoxic treatments [26].

OF does not imply only a loss of fertility (reproductive function) but also loss of estrogen production (endocrine function) by the ovaries, leading to morbidity in terms of osteoporosis, heart disease, urogenital dystrophy, vasomotor symptoms (hot flashes), psychological effects (depressive illness), and, in general, diminished quality of life [29].

Cyclophosphamide-induced OF is dose related, and there is a time-dependent effect of cyclophosphamide associated with the stage of follicle development at the time of exposure [28]. Cyclophosphamide toxicity in women may be caused by a direct effect on the oocyte or may indirectly affect the oocyte through an effect on the supporting granulosa cells of the follicle [30]. The frequency of OF secondary to cyclophosphamide administration ranges from 11% to 59% and seems to relate to patient age (older patients are more susceptible) and cumulative drug dose [26, 28].

Fertility Preservation Options

In men the most common strategy is:

- *Sperm cryopreservation* [31]. However, this is not a viable option for prepubertal patients. Moreover, testicular function can be impaired even before chemotherapy in patients with systemic disease, leading to poor sperm quality and sperm counts [26, 31].
- *GnRH-a* administered in a depot delivery produces a paradoxical desensitization of pituitary gonadotropin secretion, decreasing estrogen and progesterone to prepubertal levels, which results in a safe, effective, complete, and reversible ablation of the reproductive axis [32]. GnRH-a triptorelin coadministration may preserve fertility in women treated with cyclophosphamide [26].
- Data shows a protective effect of *testosterone* and triptorelin administration on cyclophosphamide-induced gonadal damage in men and women with various forms of nephritis, respectively [26].

Chronic renal failure leads to many metabolic disorders affecting reproductive function:

In men:

- Hypergonadotropic hypogonadism
- Hyperprolactinemia
- Spermatic alteration
- Decreased libido
- Erectile dysfunction

Kidney transplantation improves sperm parameters and hormonal function within 2 years. But sperm alterations may persist with the use of immunosuppressive drugs [33].

In women hypothalamic–pituitary–ovarian axis dysfunction due to chronic renal failure results in:

- Menstrual irregularities
- Anovulation
- Infertility

After kidney transplantation, regular menstruations usually start 1–12 months after transplantation. Fertility can be restored but luteal insufficiency can persist. Moreover, 4–20% of women with renal transplantation suffer from premature ovarian failure syndrome. In some cases, assisted reproductive technologies can be required and imply risks of ovarian hyperstimulation syndrome and must be performed with caution. Assisted reproductive technology management requires a multidisciplinary approach with obstetrics, nephrology, and reproductive medicine teams' agreement [33].

CPO was found to produce prolonged remission in patients with relapsing NS [34, 35] and was approved by the Federal Drug Administration as an anticancer agent. It continues to have significant clinical applications in nephrology, oncology, and rheumatology [36, 37]. The risk of sustained amenorrhea has been shown to develop in a dose-dependent and age-dependent pattern, with older patients and patients receiving higher cumulative doses at an increased risk of developing amenorrhea [38]. Similar protective effect of age is not noted in male patients [36].

CPO continues to be a key therapy for patients with steroid-dependent NS [34, 35] and rheumatologic diseases, including LN [36].

Alkylating agents, specifically CPO and chlorambucil, are the most effective second-line therapy in pediatric patients with steroid-sensitive NS who relapse despite steroid therapy [39]. Therapy for frequently relapsing NS with a combination of oral CPO and steroids for 8–12 weeks results in a significantly reduced risk of relapse at both the 6–12-month mark and the 12–24-month mark compared to prednisone alone [39].

The use of CPO for proliferative LN has resulted in the reduction of mortality in recent years [40]. Recent studies have also demonstrated the equivalent efficacy of mycophenolate mofetil (MMF) in inducing remission in LN [36].

The 2012 American College of Rheumatology Clinical Practice Guidelines for Lupus Nephritis established MMF as the preferred induction agent compared to CPO for patients in whom fertility preservation (FP) is a major consideration [41].

While the role of CPO in LN therapy may be evolving, at the present time, it continues to be an important drug in induction therapy for severe renal disease. While the majority of research on FP in the pediatric patient has been in the realm of oncology, a similar standard of care should be adopted for the pediatric patient with renal disease [36].

CPO is classified as an alkylating agent. The recommended dosing limit in male patients is 7.5 g/m2 based on sperm count recovery [42]. While this dosing limit is

also accepted for the female patient, the protective effect of age allows younger patients to tolerate a higher cumulative dose, up to 10–15 g/m2 [38]. While male patients develop profound oligospermia and eventually azoospermia over the course of therapy with CPO, this effect can be reversible over time in many patients, with a possibility of recovering fertility if dosing limits are maintained [36].

CPO therapy in female patients causes ovarian toxicity in an age- and dose-dependent manner [29, 43].

Since alkylating agents cause iatrogenic infertility, physicians are obligated to offer access to sperm banking in AYA (adolescent and young adult) males treated with alkylating agents. Sperm banking has the advantage of being a low-risk procedure with moderate cost and a reasonable rate of subsequent successful pregnancy in AYA males at Tanner III stage of development or greater. Adolescent patients who bank sperm report that they felt positively about attempting to provide a sperm sample regardless of success or failure. There are no standards of practice that govern the use of sperm banking among AYA males outside of the oncology population, even when alkylating agents are used. We need to offer a well-established fertility preservation therapy for all iatrogenic fertility compromising disorders [44].

Nephrotic Syndrome

It is a rare disease in children, with an incidence of 2–7 cases per 100,000; four or 10–30% of children with nephrotic syndrome have steroid-dependent disease (steroid-dependent nephrotic syndrome (SDNS)) potentially requiring treatment with CPO [45]. Pediatric nephrologists attempt to keep doses of CPO under the established limit of gonadotoxicity for males of between 168 and 250 mg/kg [45].

If nephrologists use a drug that can cause gonadotoxicity, then they have an obligation to mitigate this side effect by sperm banking. Existing research shows great individual variability among patients, some of whom suffer permanent sterility at low CPO doses [42, 46]. Given the duty to protect patient fertility when using a drug like CPO and the flimsiness of potential arguments against the use of sperm banking, it seems that AYA males with SDNS who are treated with CPO should be offered access to sperm banking. Pediatric and adult nephrologists have patients with glomerulonephritis caused by pauci-immune vasculitis and systemic lupus erythematosus, who are treated with CPO [45]. Patients with rheumatological diseases treated with CPO could be considered on similar grounds. More discussion is needed to determine who should routinely have access to fertility-saving technology, especially outside of oncology in fields such that any patient exposed to gonadotoxic agents should be offered access to sperm banking. As other strategies for fertility preservation such as oocyte cryopreservation and ovarian tissue storage evolve [47], they also may need to be routinely offered to those whose fertility is lost or compromised due to treatment [44].

Sperm banking is a well-established, effective, and accepted practice for collecting and storing male gametocytes in adolescent patients who are at Tanner III stage of development or greater [48].

If a patient is unable to produce sample, alternative sources include:

- Microsurgical *epididymal aspiration*
- *Electroejaculation*
- *Testicular biopsy*, although there has been success with fertilization in animal models, preserved testicular tissue has not yet been demonstrated to be successful for spermatogenesis in humans [36].

New methods for in vitro fertilization (IVF) include intrauterine insemination (IUI) and intracytoplasmic sperm injection (ICSI), and these methods have improved fertility outcomes for men with low sperm counts or motility defects [36].

All teenage boys whose therapy will include CPO should be given the opportunity to cryopreserve sperm regardless of their planned dose of CPO. Doses of CPO are sometimes extended in refractory renal disease, so it is not always possible to accurately predicate a cumulative exposure in these patients [36].

Options for FP in the prepubescent male are limited to experimental protocols. The goal of FP in patients who have not yet undergone spermatogenesis is preservation of *spermatogonial stem cells (SSCs)*. SSCs can be isolated from aspirated cell suspension or from *cryopreserved immature testicular tissue* (ITT). The advantage of ITT cryopreservation is the maintenance of tissue architecture and cell-to-cell contacts between Sertoli cells and germinal stem cells, which eventually become important for the maturation of SSC [49].

Emerging techniques include oocyte cryopreservation with vitrification of both mature and immature oocytes, thereby allowing the storage of an unfertilized egg. The introduction of *cryopreservation of ovarian* tissue through experimental protocols has the potential to expand the availability of assisted reproductive technology to premenstrual females [36].

Sexual Effects

Sexual dysfunction resulting from general lack of interest in sexual activity is also common among women with ESRD and may be caused by medication side effects, fatigue, symptoms of depression, and altered body image owing to the presence of catheters or fistulas.

Surveys performed on patients with end-stage kidney failure identified a high rate of sexual dysfunction [50, 51]. Women frequently complain of decreased libido, problems with lubrication, and an inability to achieve orgasm [52]; other studies indicate that sexual dysfunction is less prevalent in transplant patients than in the dialysis population [53, 54], and the reported frequency of sexual intercourse is more common in the transplant patient than the patient on dialysis [10, 55]. Sexual dysfunction is common in kidney transplant recipients [10].

Patients with end-stage chronic kidney failure (CKF) who undergo hemodialysis experience a significant deterioration in their quality of life, due both to a treatment

requiring patients to attend dialysis sessions of 3–4 h duration 3 days a week and to the comorbidity associated with it [44].

Among comorbidities, it is important to highlight erectile dysfunction due to its high-frequency erectile dysfunction (ED) that is an inability to obtain or maintain an erection sufficient for satisfactory sexual activity [44].

Several factors may contribute to the onset of erectile dysfunction and its progression over time. These could include abnormalities in the neuroendocrine control system of the hypothalamic–pituitary–gonadal axis, secondary hyperparathyroidism, peripheral neuropathy, changes in smooth muscle of the corpora cavernosa of the penis, structural alterations of the arterial wall, damage of the veno-occlusive cavernosal mechanism, drug therapies consequential to CKF, stress, and depression [44].

It is not surprising that the prevalence rate of erectile dysfunction in dialyzed patients could be as high as 80%. In kidney transplanted patients, the prevalence of erectile dysfunction remains high, occurring in around 65% of cases, and hypogonadism is also a frequent occurrence. The protracted uremic condition before the transplant is not only due to a functional damage but also to an anatomical damage to the delicate hypothalamic–pituitary–gonadal axis. In hypogonadism which is significantly lower among transplant recipients, the kidney transplantation appears to have a protective role of the sexual capabilities of these patients. In fact, there is increasingly more scientific evidence indicating that low testosterone serum level correlates with increased cardiovascular accidents, increased central obesity, metabolic syndrome, and bone fragility which would reduce life expectancy [44].

Immunosuppression

Chronic kidney disease (CKD) is associated with infertility as a result of hypogonadotropic hypogonadism and not POI, yet the treatment of CKD depends on the etiology and can involve the use of alkylating-based chemotherapy, known to be gonadotoxic [56].

Further complicating the issue of infertility in patients with CKD is the prevalence of sexual dysfunction from uremia and psychogenic, neurogenic, vascular, or disease-related comorbidities [56–59]; the expanded use of home HD allows for the greater flexibility that most young women need to be able to adequately increase intensity so that fertility can be enhanced, making pregnancy both possible and successful [56].

Fertility in Women on Dialysis and After Successful Transplantation

It is believed that the lack of estradiol-stimulated cyclic LH secretion in women on dialysis leads to ovarian failure (anovulation), which is presumed to be the primary cause of infertility [7].

Nocturnal home hemodialysis may also restore a more normal hormonal milieu in women on dialysis [7].

Similar to men, successfully transplanted women have less infertility and more normal hormonal levels of prolactin, LH, follicle-stimulating hormone (FSH), and estradiol [7].

Fertility in Men on Dialysis and After Successful Kidney Transplant

Transplantation defects in gonadotropin and pituitary and hypothalamic function are all involved and contribute to the impaired fertility observed in men and women with CKD. Men on dialysis have reduced numbers of mature spermatocytes, decreased sperm counts, and poorly functioning sperm, pointing to an evidence of impaired spermatogenesis [60, 61]. In addition, because of impaired Leydig cell production, free testosterone levels are often low. The low testosterone level results in an increase in LH and a reduced and delayed response to human chorionic gonadotropin stimulation [60, 61]. After successful kidney transplantation, serum testosterone and LH levels are usually restored to normal [62].

Sperm density, motility, viability, and morphology also significantly improved 4 months after transplantation. The implication is that nocturnal home hemodialysis somehow normalizes the hormonal milieu of ESRD. If additional study confirms these findings, fertility of men and women on nocturnal hemodialysis may be significantly better than those on conventional hemodialysis and may approach that of successfully transplanted patients [7].

Infertility is common, poorly studied, and caused by multiple factors in men and women with CKD [15].

Fertility is impaired in men and women on dialysis, and probably also in those with CKD, but it is restored with successful kidney transplantation. Nocturnal home hemodialysis may lead to improved fertility compared with conventional dialysis. The causes of infertility in ESRD/CKD patients are complex and due in part to sexual dysfunction (lack of libido, impotence) and alterations in the normal hormonal milieu. It is clear that sexual dysfunction and fertility remain important issues to men and women with kidney disease [15].

References

1. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis Off J Nat Kidney Found. 2014;63(5):713–35.
2. Piccoli GB, Cabiddu G, Attini R, Vigotti F, Fassio F, Rolfo A, et al. Pregnancy in chronic kidney disease: questions and answers in a changing panorama. Best Pract Res Clin Obstet Gynaecol. 2015;29(5):625–42.

3. Sherwood M, McCullough PA. Chronic kidney disease from screening, detection, and awareness, to prevention. Lancet Glob Health. 2016;4(5):e288–e9.
4. Himmelfarb J, Sayegh MHS. Chronic kidney disease: definition, epidemiology, cost, and outcomes. In: Chandraker A, Mehrotra R, O'Hare AM, Stivelman JC, Tuttle KR, Vella JP, et al., editors. Chronic kidney disease, dialysis, and transplantation. 3rd ed. Philadelphia: ELSEVIER; 2010.
5. Davison JM, Lindheimer MD. Pregnancy and chronic kidney disease. Semin Nephrol. 2011;31(1):86–99.
6. Tong A, Brown MA, Winkelmayer WC, Craig JC, Jesudason S. Perspectives on pregnancy in women with CKD: a semistructured interview study. Am J Kidney Dis Off J Nat Kidney Found. 2015;66(6):951–61.
7. Holley JL, Schmidt RJ. Changes in fertility and hormone replacement therapy in kidney disease. Adv Chronic Kidney Dis. 2013;20(3):240–5.
8. McKay DB, Josephson MA. Pregnancy in recipients of solid organs--effects on mother and child. N Engl J Med. 2006;354(12):1281–93.
9. Williams D, Davison J. Chronic kidney disease in pregnancy. BMJ (Clin Res Ed). 2008;336(7637):211–5.
10. Josephson MA, McKay DB. Women and transplantation: fertility, sexuality, pregnancy, contraception. Adv Chronic Kidney Dis. 2013;20(5):433–40.
11. Chakhtoura Z, Meunier M, Caby J, Mercadal L, Arzouk N, Barrou B, et al. Gynecologic follow up of 129 women on dialysis and after kidney transplantation: a retrospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2015;187:1–5.
12. Lim VS, Henriquez C, Sievertsen G, Frohman LA. Ovarian function in chronic renal failure: evidence suggesting hypothalamic anovulation. Ann Intern Med. 1980;93(1):21–7.
13. Lim VS, Kathpalia SC, Frohman LA. Hyperprolactinemia and impaired pituitary response to suppression and stimulation in chronic renal failure: reversal after transplantation. J Clin Endocrinol Metab. 1979;48(1):101–7.
14. Matuszkiewicz-Rowinska J, Skorzewska K, Radowicki S, Niemczyk S, Sokalski A, Przedlacki J, et al. Endometrial morphology and pituitary-gonadal axis dysfunction in women of reproductive age undergoing chronic haemodialysis--a multicentre study. Nephrol Dial Transplant Off Pub Eur Dial Transplant Assoc Eur Ren Assoc. 2004;19(8):2074–7.
15. Holley JL, Reddy SS. Pregnancy and CKD: lessons on communication from patients. Am J Kidney Dis Off J Nat Kidney Found. 2015;66(6):936–8.
16. Framarino Dei Malatesta M, Rossi M, Rocca B, Iappelli M, Poli L, Piccioni MG, et al. Fertility following solid organ transplantation. Transplant Proc. 2007;39(6):2001–4.
17. Hladunewich M, Schatell D. Intensive dialysis and pregnancy: Hemodial Int. 2016;20(3):337–494, E1–E18.
18. Lopez LF, Martinez CJ, Castaneda DA, Hernandez AC, Perez HC, Lozano E. Pregnancy and kidney transplantation, triple hazard? Current concepts and algorithm for approach of preconception and perinatal care of the patient with kidney transplantation. Transplant Proc. 2014;46(9):3027–31.
19. ter Haar-van Eck SA, Rischen-Vos J, Chadha-Ajwani S, Huikeshoven FJ. The incidence of cervical intraepithelial neoplasia among women with renal transplant in relation to cyclosporine. Br J Obstet Gynaecol. 1995;102(1):58–61.
20. Brunner FP, Landais P, Selwood NH. Malignancies after renal transplantation: the EDTA-ERA registry experience. European Dialysis and Transplantation Association-European Renal Association. Nephrol Dial Transplant Off Publ Eur Dial Transplant Assoc Eur Ren Assoc. 1995;10 Suppl 1:74–80.
21. Filocamo MT, Zanazzi M, Li Marzi V, Lombardi G, Del Popolo G, Mancini G, et al. Sexual dysfunction in women during dialysis and after renal transplantation. J Sex Med. 2009;6(11):3125–31.

22. Pietrzak B, Wielgos M, Kaminski P, Jabiry-Zieniewicz Z, Bobrowska K. Menstrual cycle and sex hormone profile in kidney-transplanted women. Neuro Endocrinol Lett. 2006;27(1–2):198–202.
23. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis Off J Nat Kidney Found. 1998;32(5 Suppl 3):S112–9.
24. Kim JH, Chun CJ, Kang CM, Kwak JY. Kidney transplantation and menstrual changes. Transplant Proc. 1998;30(7):3057–9.
25. Cochrane R, Regan L. Undetected gynaecological disorders in women with renal disease. Hum Reprod (Oxford, England). 1997;12(4):667–70.
26. Cigni A, Faedda R, Atzeni MM, Pileri PV, Alagna S, Rovasio P, et al. Hormonal strategies for fertility preservation in patients receiving cyclophosphamide to treat glomerulonephritis: a nonrandomized trial and review of the literature. Am J Kidney Dis Off J Nat Kidney Found. 2008;52(5):887–96.
27. Howell SJ, Shalet SM. Testicular function following chemotherapy. Hum Reprod Update. 2001;7(4):363–9.
28. Raptopoulou A, Sidiropoulos P, Boumpas D. Ovarian failure and strategies for fertility preservation in patients with systemic lupus erythematosus. Lupus. 2004;13(12):887–90.
29. Blumenfeld Z, Avivi I, Linn S, Epelbaum R, Ben-Shahar M, Haim N. Prevention of irreversible chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy. Hum Reprod (Oxford, England). 1996;11(8):1620–6.
30. Kreuser ED, Klingmuller D, Thiel E. The role of LHRH-analogues in protecting gonadal functions during chemotherapy and irradiation. Eur Urol. 1993;23(1):157–63. discussion 63-4
31. Pendse S, Ginsburg E, Singh AK. Strategies for preservation of ovarian and testicular function after immunosuppression. Am J Kidney Dis Off J Nat Kidney Found. 2004;43(5):772–81.
32. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis Rheum. 2005;52(9):2761–7.
33. Delesalle AS, Robin G, Provot F, Dewailly D, Leroy-Billiard M, Peigne M. Impact of end-stage renal disease and kidney transplantation on the reproductive system. Gynecol Obstet Fertil. 2015;43(1):33–40.
34. Kyrieleis HA, Levtchenko EN, Wetzels JF. Long-term outcome after cyclophosphamide treatment in children with steroid-dependent and frequently relapsing minimal change nephrotic syndrome. Am J Kidney Dis Off J Nat Kidney Found. 2007;49(5):592–7.
35. White RH. Cytotoxic drug therapy in steroid-resistant glomerulonephritis. Proc R Soc Med. 1967;60(11 Part 1):1164–8.
36. Gajjar R, Miller SD, Meyers KE, Ginsberg JP. Fertility preservation in patients receiving cyclophosphamide therapy for renal disease. Pediatr Nephrol (Berlin, Germany). 2015;30(7):1099–106.
37. Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. Nat Rev Clin Oncol. 2009;6(11):638–47.
38. Boumpas DT, Austin 3rd HA, Vaughan EM, Yarboro CH, Klippel JH, Balow JE. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Ann Intern Med. 1993;119(5):366–9.
39. Pravitsitthikul N, Willis NS, Hodson EM, Craig JC. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Database Syst Rev. 2013;10:Cd002290.
40. Vaz-Carneiro A, Costa J. Analysis of the cochrane review: electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev. 2014,12: CD010216. Acta Med Port. 2015;28(2):145–7.
41. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012;64(6):797–808.

42. Meistrich ML, Wilson G, Brown BW, da Cunha MF, Lipshultz LI. Impact of cyclophosphamide on long-term reduction in sperm count in men treated with combination chemotherapy for Ewing and soft tissue sarcomas. Cancer. 1992;70(11):2703–12.
43. Ethics Committee of the American Society for Reproductive. Medicine Fertility preservation and reproduction in cancer patients. Fertil Steril. 2005;83(6):1622–8.
44. Miller SD, Ginsberg JP, Caplan A, Meyers KE. Sperm banking in adolescent males with nephrotic syndrome: defining the limits of access to fertility preservation. Arch Dis Child. 2012;97(9):765–6.
45. Hodson EM, Willis NS, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database Syst Rev. 2010;11:cd003594.
46. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol (Berlin, Germany). 2001;16(3):271–82.
47. Patrizio P, Butts S, Caplan A. Ovarian tissue preservation and future fertility: emerging technologies and ethical considerations. J Natl Cancer Inst Monogr. 2005;34:107–10.
48. Ginsberg JP, Ogle SK, Tuchman LK, Carlson CA, Reilly MM, Hobbie WL, et al. Sperm banking for adolescent and young adult cancer patients: sperm quality, patient, and parent perspectives. Pediatr Blood Cancer. 2008;50(3):594–8.
49. Wyns C, Curaba M, Vanabelle B, Van Langendonckt A, Donnez J. Options for fertility preservation in prepubertal boys. Hum Reprod Update. 2010;16(3):312–28.
50. Diemont WL, Vruggink PA, Meuleman EJ, Doesburg WH, Lemmens WA, Berden JH. Sexual dysfunction after renal replacement therapy. Am J Kidney Dis Off J Nat Kidney Found. 2000;35(5):845–51.
51. Raiz L, Davies EA, Ferguson RM. Sexual functioning following renal transplantation. Health Soc Work. 2003;28(4):264–72.
52. Muehrer RJ. Sexuality, an important component of the quality of life of the kidney transplant recipient. Transplant Rev (Orlando). 2009;23(4):214–23.
53. Basok EK, Atsu N, Rifaioglu MM, Kantarci G, Yildirim A, Tokuc R. Assessment of female sexual function and quality of life in predialysis, peritoneal dialysis, hemodialysis, and renal transplant patients. Int Urol Nephrol. 2009;41(3):473–81.
54. Navaneethan SD, Vecchio M, Johnson DW, Saglimbene V, Graziano G, Pellegrini F, et al. Prevalence and correlates of self-reported sexual dysfunction in CKD: a meta-analysis of observational studies. Am J Kidney Dis Off J Nat Kidney Found. 2010;56(4):670–85.
55. Noohi S, Azar M, Behzadi AH, Barbati ME, Haghshenas A, Amoozgar B, et al. Comparison of sexual function in females receiving haemodialysis and after renal transplantation. J Ren Care. 2010;36(4):212–7.
56. Hirshfeld-Cytron J, Gracia C, Woodruff TK. Nonmalignant diseases and treatments associated with primary ovarian failure: an expanded role for fertility preservation. J Womens Health (Larchmt). 2011;20(10):1467–77.
57. Anantharaman P, Schmidt RJ. Sexual function in chronic kidney disease. Adv Chronic Kidney Dis. 2007;14(2):119–25.
58. Levy DP, Giatras I, Jungers P. Pregnancy and end-stage renal disease--past experience and new insights. Nephrol Dial Transplant Off Publ Eur Dial Transplant Assoc Eur Ren Assoc. 1998;13(12):3005–7.
59. Guazzelli CA, Torloni MR, Sanches TF, Barbieri M, Pestana JO. Contraceptive counseling and use among 197 female kidney transplant recipients. Transplantation. 2008;86(5):669–72.
60. Lim VS. Reproductive function in patients with renal insufficiency. Am J Kidney Dis Off J Nat Kidney Found. 1987;9(4):363–7.
61. Handelsman DJ, Dong Q. Hypothalamo-pituitary gonadal axis in chronic renal failure. Endocrinol Metab Clin North Am. 1993;22(1):145–61.
62. Akbari F, Alavi M, Esteghamati A, Mehrsai A, Djaladat H, Zohrevand R, et al. Effect of renal transplantation on sperm quality and sex hormone levels. BJU Int. 2003;92(3):281–3.

Chapter 11
Premature Ovarian Insufficiency

Incidence

The prevalence of premature ovarian insufficiency (POI) is 1%; population characteristics such as ethnicity may affect the prevalence [1, 2]. Premature menopause was reported by 1% of Caucasians, 1.4% of African Americans and Hispanics, 0.5% of Chinese, and 0.1% of Japanese women [2, 3].

Definition

POI is a clinical syndrome defined by loss of ovarian activity before the age of 40 years, characterized by amenorrhea of more than 4 months with increased FSH and low estradiol, traditionally defined as hypergonadotropic hypogonadism [1, 2, 4, 5].

Because approximately 50% of women with primary ovarian insufficiency have intermittent ovarian function leading to intermittent and unpredictable menses, rather than complete amenorrhea, a more practical definition is 4 months or more of "disordered" menses (amenorrhea, oligomenorrhea, polymenorrhea, or metrorrhagia) in association with menopausal FSH levels [4].

POI is defined by a triad of signs:

(i) Amenorrhea or disordered menses for at least 4 months
(ii) Decreased estradiol serum concentrations
(iii) Elevated follicle-stimulating hormone (FSH) serum concentrations (more than 40 IU/l in at least two samples 1 month apart) [6–8]

POI typically ends in premature depletion of the follicular pool; it may occur before menarche or any time before the age of 40 [9]. Although menstrual cycles cease in these patients, some of them still contain residual small ovarian follicles not

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_11

producing enough circulating estrogens and progesterone to modulate uterine functions [7].

The presumption of ovarian failure is evidenced by the association between decreased natural fecundity and lowered assisted reproductive technology success rates with increased FSH concentrations and increased age.

Natural History

In 90% of the cases of primary ovarian insufficiency, the cause remains a mystery [4]. Evidence implicating a number of genetic factors is growing rapidly [2, 10].

The development of POI might be explained by either:

- Diminished ovarian reserve at birth
- Accelerated rate of primordial follicle recruitment
- Increased atresia (depletion) of the follicles or a follicular dysfunction [11]

Follicle dysfunction indicates that follicles remain in the ovary, but a pathologic process prevents their normal function (e.g., as a result of an FSH receptor mutation).

Follicle depletion indicates that no primordial follicles remain in the ovary. This condition may be due to the failure of an adequate initial pool of primordial follicles to be established in the utero, an accelerated expenditure of follicles, or autoimmune or toxic destruction of follicles [4]. Premature follicular depletion is the cause in almost all cases (exhaustion of the pool of primordial follicles is the cause of POI in most women) [5].

Etiology

In patients with POI, the loss of oocytes and fertility potential is associated sometimes with exposure to systemic chemotherapy, pelvic irradiation, genetic abnormalities (e.g., 45,X chromosomal mosaicism, FMR1 permutations), and autoimmune disorders. In a significant number of women with POI, the cause is not identified, and these women are described as having unexplained or idiopathic POI [1]; 50–65% of cases are idiopathic [2, 7, 9, 12, 13].

Although most cases of primary ovarian insufficiency occur sporadically, sometimes there is a positive family history and suggesting a genetic etiology which is found in only 25% of cases [9]. A few genes have been associated with POI [5, 12]. A family history of the fragile X syndrome, intellectual disability, dementia, tremor or ataxia, or symptoms similar to those associated with Parkinson's disease might point to a permutation in the fragile X mental retardation 1 (FMR1) gene [4, 14]. Thus, patients should be queried about family history as well as about autoimmune disorders that might relate to an autoimmune polyglandular syndrome.

Disease Presentation

POI needs to be excluded in women with amenorrhea/oligomenorrhea or estrogen-deficiency symptoms below the age of 40 years [1, 4]. In most of the women affected, there are no signs or symptoms that precede the interruption of menstruation and the onset of POI, and the majority of women have a normal history of menarche, regular menstrual cycles, and normal fertility (POI generally results in secondary amenorrhea) [15] but also may occur at any time before menarche [2].

The potential causes of secondary amenorrhea are long; the majority of cases are accounted for by four conditions:

- Polycystic ovary syndrome
- Hypothalamic amenorrhea
- Hyperprolactinemia
- Primary ovarian insufficiency

It is inappropriate to attribute amenorrhea to stress without further evaluation.

Diagnosis

Physical examination

It is important to focus on body form, evidence of normal secondary sexual characteristics, and breast development.

In young females, it is important to evaluate amenorrhea or a change from regular to irregular menses for 3 or more consecutive months in the absence of hormonal influence such as oral contraceptives, for all potential causes:

- Pregnancy
- Thyroid abnormalities
- Hyperprolactinemia
- Polycystic ovary syndrome
- Hypothalamic amenorrhea
- Premature ovarian insufficiency [15]

Laboratory Evaluation

- Measurements of basal FSH and estradiol levels samples, FSH on CD 2–5 (prior to starting stimulation in patients)
- Anti-Mullerian hormone (any day of menstrual cycle)
- Transvaginal ultrasound scan of the ovaries' ovarian follicle count (performed on CD 2–5) [15]

Further Testing

Once a diagnosis of POI is established, further testing in order to investigate the possible etiology of POI is necessary [15, 16]:

- Karyotyping (in particular in women less than 30 years of age)
- Adrenal antibodies (with the use of indirect immunofluorescence or 21-hydroxylase [CYP21] immunoprecipitation)
- Testing of FMR1 premutation
- The measurement of bone mineral density [4] should be considered for all women with POI diagnosis but especially when there are additional risk factors [17]

Biochemical and other hormonal analysis such as free thyroxin, TSH, prolactin, and testosterone is recommended, and an ultrasound scan of the breasts and the pelvis are advisable [15].

Causes of POI
Idiopathic causes 65%
Family recurrence 20%
Autoimmune diseases 10%
Genetic disorders 5% [15]

Genetic disorders
The possible genetic role in the development of POI has been largely demonstrated, and many genes have been involved. Heritability has been demonstrated, ranging from 30% to 85%; in fact the onset of menopause before 45 years is four- to ninefold more frequent if one other family member such as the mother, sister, or grandmother is affected by POI. A genetic assessment could be useful to identify genes and pathways involved in POI, and if a genetic alteration is found, it can be an important discussion for family counseling to plan for future reproductive activity [15]. Chromosomal analysis should be performed in all women with non-iatrogenic POI [18–20]. Numerical and structural chromosomal abnormalities may be identified on these patients [2]. Karyotype should be obtained to exclude chromosomal translocations, deletions, mosaicism, and sex chromosomal abnormalities, as well as Turner syndrome (if positive, refer to endocrinologist, cardiologist, and geneticist) and mosaic Turner syndrome.

45, X/46,XX. A karyotype also identifies those having a Y chromosome in whom gonadectomy is indicated due to the significant risk for malignant transformation in occult testicular elements (20–30%) [21]. Many experts suggest checking the karyotype in women who are younger and have never been pregnant. The value of chromosome analysis is diminished in women who are older than 30–35 years old and have had a child [15, 22]; also most tumors in patients with a Y chromosome arise before age 20 and virtually all before the age of 30 [23, 24]. After age 30, women with short stature or a family history of early menopause still merit a karyotype to exclude X chromosome deletions and translocations that may affect other family members [2, 25, 26].

Evidence has demonstrated an association between premature ovarian insufficiency (POI) and fragile X "premutations"; women who carry fragile X premutations are at risk for having a child with fragile X syndrome, therefore should receive formal genetic counseling [1, 2, 18, 27]. Fragile X carrier screening is recommended to all women with POI by the American College of Obstetricians and Gynecologists [22] (see Fragile X-associated Primary Ovarian Insufficiency) (FXPOI)—See more

at: http://oncofertility.northwestern.edu/resources/fragile-x-associated-primary-ovarian-insufficiency-fxpoi#sthash.EgRe3hZw.dpuf.

Autoimmune Diseases

The ovary is not protected immunologically, and the detection of autoantibodies directed against various ovarian targets strongly supports the hypothesis of an autoimmune etiology [15].

The most common autoimmune diseases associated with POI are hypothyroidism, type I diabetes mellitus, hyperparathyroidism, Addison's disease, myasthenia gravis, thymic hypoplasia/aplasia, Crohn's disease, vitiligo, pernicious anemia, dry eye syndrome, systemic lupus erythematosus, rheumatoid arthritis, and type I and type II autoimmune polyglandular failure syndrome. In all these conditions, both premature follicular depletion and follicular dysfunction could be present [2, 15, 22].

Addison's disease (autoimmune adrenocortical insufficiency) has the strongest association with POI; this association between autoimmune adrenal and ovarian failure justifies screening for anti-adrenal antibodies in all women with POI, at the time of diagnosis [2]. Refer POI patients with a positive 21OH-Ab/ACA test to an endocrinologist for testing of adrenal function and to rule out Addison's disease, and retest in case of clinical signs or symptoms [28–32]; also patients with negative tests for adrenal antibodies should be followed and monitored with repeat testing at intervals, because POI may precede onset of adrenal insufficiency by up to several years, and its autoimmune cause may not, at first, be recognized [33]. The presence of anti-adrenal antibodies strongly implies autoimmune oophoritis as the cause of POI and identifies women who should be carefully evaluated and followed to exclude adrenal insufficiency [2].

Women with POI should be tested for *antithyroid antibodies* (antithyroid peroxidase and antithyroglobulin antibodies). In patients with a positive TPO-Ab test, thyroid-stimulating hormone (TSH) should be measured every year [1, 34–36] because the prevalence of thyroiditis is relatively high among women with POI (14–27%), and the presence of thyroid autoantibodies identifies patients at risk for developing autoimmune thyroid disease; screening for thyroid peroxidase and thyroglobulin antibodies also is indicated. The presence of thyroid autoantibodies does not prove autoimmune ovarian failure but identifies women at risk for developing autoimmune thyroid disorders [2].

Autoimmune oophoritis may occur as part of a *type I or II autoimmune polyglandular syndrome (APS)* associated with autoantibodies to multiple endocrine and other organs [2].

Cancer Treatments

Cancer treatments are a well-established cause of POI [37]. Women who have had cancer are at an increased risk of early menopause and primary ovarian insufficiency as a result of ovarian follicle depletion, stromal fibrosis, and vascular injury after chemotherapy and radiotherapy [38, 39]. Patient's age, specific cancer type, and fertility status prior to starting cancer treatment are important predictive factors of how devastating a treatment may be to fertility [40]. Younger patients can tolerate larger doses of irradiation and chemotherapy compared with older patients before

manifesting menopausal or infertility symptoms, likely because they have a larger starting follicle pool.

Radiotherapy

The adverse effects and reproductive consequences of radiation on the ovary depend on the age of the patient, dose of radiation, site, and duration of exposure, frequency of treatments, ovarian reserve before treatment, and whether or not it is administered in isolation or in combination with chemotherapy [39, 41–44] . In young women, radiation therapy may result only in transient amenorrhea that ends after a period of 6–18 months, probably reflecting the interval required to reestablish the mechanisms that govern the initiation of follicular growth and the size of their follicular reserve. However, some will suffer immediate and irreversible ovarian failure, and even those who recover may later exhibit an early ovarian aging and an early menopause. When the radiation field excludes the pelvis, there is no significant risk for permanent ovarian failure [45]. Consequently, direct irradiation to the ovaries should be avoided whenever possible. In general, actively dividing cells are more susceptible to radiation-induced death, and because oocytes in the young adult are arrested in prophase of meiosis I, they are more resistant to radiation than cells in mitosis. Primordial follicles, which are considered to be quiescent, appear to be more resistant to radiation compared with growing follicles [42]. Nevertheless, the human oocyte is indeed sensitive to radiation therapy [46]. Elective ovarian transposition (moving the ovaries out of the radiation field) can help to preserve gonadal function in patients receiving pelvic radiation; without chemotherapy, radiotherapy could cause follicular apoptosis and determine the reduction of the total pool of oocytes; obviously, if the radiotherapy is not direct to the pelvic target, the risk of POI is reduced [15, 47]. Radiation, particularly targeting the cranium, can cause an altered hypothalamus and pituitary function [42, 46, 48, 49]. Follicle depletion is the hallmark of ovarian damage and is most pronounced in those who receive total body irradiation before hemopoietic stem cell transplantation or direct irradiation of the ovaries [39].

Chemotherapy

The ovary is also chemosensitive. Chemotherapy is a relatively common cause of POI; it causes depletion of the primordial follicular pool. Chemotherapeutic drugs might directly damage the growing oocyte or the highly proliferative granulosa cells within the developing follicle [38, 39]. Effects of chemotherapy are highly dependent on the type of drug used, the dose, the frequency, and the treatment duration [46, 50, 51]. Alkylating agents, especially cyclophosphamide and busulfan, are more gonadotoxic compared with other chemotherapeutics, including platinum agents, plant alkaloids, and antimetabolites [50, 52, 53]. Alkylating agents produce DNA breaks irrespective of cell cycle stage and have a high risk for targeting primordial follicles for death and also of compromising stromal cell function [46, 54].

Follicle destruction, whether by radiation- or chemotherapy-induced mechanisms, does not simply lead to gamete loss but can also result in impaired ovarian hormone production and uterine dysfunction. Although follicles may resist cancer therapies, the ovarian reserve may be compromised and depleted early [46].

Other Causes

Functional ovarian failure resulting from disorders of follicular development whereas accelerated follicular depletion is the underlying mechanism for the most common causes of POI, a variety of rare genetic disorders causing impaired or abnormal follicular development may result in a functional ovarian failure. Examples include disorders of intraovarian regulation, steroidogenic enzyme defects, and abnormalities in gonadotropins and their receptors.

Disease Management

Attention should focus first on excluding those causes of POI having important potential health consequences for the patient or other members of her family. Those with chromosomal translocations or deletions or fragile X premutations should receive appropriate genetic counseling, and those with autoimmune disease will require careful monitoring over time to ensure that emerging and potentially serious health problems are promptly recognized and treated.

It is important to emphasize that effective management of POI requires careful counseling and emotional support, as well as specific evaluation and medical treatment. Young women with POI are not prepared for the diagnosis [2]. Affected women need, and deserve, sufficient time for thorough education and for planning their longer-term management.

Long-term consequences of premature ovarian failure:

- Infertility
- Psychological distress and depression
- Decreased sexual and general well-being
- Autoimmune disorders
- Osteoporosis
- Ischemic heart disease
- Increased risk for mortality [22]

Ovarian function encompasses both the fertility and the endocrine benefits of ovarian steroids. The loss of ovarian function can negatively impact bone health, cardiovascular health, and sexual function [37].

Bone Protection and Improvement

It is important to consider bone health at diagnosis in POI and during ongoing care. POI is associated with reduced bone mineral density (BMD) [18, 55–58]; this indicates that it is associated with an increased risk of fracture later in life [1, 18, 31, 55–63]. Women should maintain a healthy lifestyle, involving weight-bearing exercise, avoidance of smoking, and maintenance of normal body weight to optimize

bone health. A balanced diet will contain the recommended intake of calcium and vitamin D. Dietary supplementation may be required in women with inadequate vitamin D status and/or calcium intake and may be of value in women with low BMD [64, 65].

Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture [17, 66, 67]. The combined oral contraceptive pill may be appropriate for some women, but effects on BMD are less favorable [68]. Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy [1, 69, 70].

Cardiovascular System Protection

Women with POI are at increased risk of cardiovascular disease and should be advised of risk factors that they can modify through behavioral change (e.g., stopping smoking, taking regular weight-bearing exercise, healthy weight) [1, 71–74]. Hormone replacement therapy (HRT) with early initiation is strongly recommended in women with POI to control future risk of cardiovascular disease; it should be continued at least until on the average age of natural menopause [75–78]. At least blood pressure, weight, and smoking status should be monitored annually with other risk factors being assessed if indicated [1]. Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease [71, 79–82].

Treatment Needs to Focus on Psychological Well-Being and Quality of Life

Lifestyle and Dietary Interventions

Women with POI should be advised to take lifestyle measures to reduce possible risks for cognitive impairment.

Although no causal relation has been proved for cigarette smoking and POI, there is a relation to early menopause; therefore, women who are prone to POI should be advised to stop smoking [1].

A diagnosis of POI has a significant negative impact on psychological well-being and quality of life [83, 84].

Psychological and lifestyle interventions should be accessible for them [1, 85–88]. It is also important to emphasize that the diagnosis of POI does not imply or predict premature aging in any other way, something that many women understandably may fear. Women with POI also are at risk for developing related depression and anxiety disorders [89, 90]. Consequently, referral to a support group

(www.pofsupport.org) and to a therapist having expertise in counseling women and couples with reproductive failure can be very helpful [22].

Treatment for Consequences of POI for Sexuality

Routinely inquire about sexual well-being and sexual function in women with POI [1]. Adequate estrogen replacement is regarded as a starting point for normalizing sexual function. Local estrogen may be required to treat dyspareunia [1, 91]. Cancer therapies can diminish a woman's sense of sexuality. Increased menopausal symptoms, including vaginal dryness and hot flushes, could lead to sexual dysfunction, and body changes due to surgery could lead to a loss of identity or attractiveness [46, 92–95]. Female cancer survivors show evidence of greater sexual dysfunction and lower quality of life compared with noncancer-afflicted infertile women [92]. It is important to provide cancer patients with specific information and care regarding their reproductive function in light of their cancer diagnosis [46].

Treatment of Genitourinary Symptoms in POI

Clinicians should be aware that women with POI may experience genitourinary symptoms. Local estrogens are effective in the treatment of genitourinary symptoms [96] and may be given in addition to systemic HRT [91]. Lubricants are useful for the treatment of vaginal discomfort and dyspareunia for women not using HRT [1, 97, 98].

Medical Treatment

Hormone Therapy

HRT is indicated for the treatment of symptoms of low estrogen in women with POI [99–101]. Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection [1, 17, 75–78, 102, 103]. Inevitably, they also will develop symptoms of estrogen deficiency such as vasomotor flushes and genitourinary atrophy that can be debilitating. Therefore, unless there is a specific contraindication to its use, women with POI should receive exogenous estrogen therapy.

Estrogen treatment in women with POI can take several forms. Physiologic levels of estrogen can be achieved using oral cyclic or continuous treatment. A progestogen should be given in combination with estrogen therapy to protect the

endometrium and prevent endometrial hyperplasia and neoplasia that can result from treatment with estrogen alone in women with an intact uterus [1, 104, 105]; the strongest evidence of endometrial protection is for oral cyclical combined treatment (for 10–12 days each month) [15]. Hormone therapy should continue up to at least the age of 50, the same way as endogenous hormone production does in normal women. HRT has not been found to increase the risk of breast cancer before the age of natural menopause [82, 106, 107]. 17-β estradiol is preferred than ethinylestradiol or conjugated equine estrogens for estrogen replacement [68, 77].

Transdermal, oral, or transvaginal estradiol in doses of 100 μg daily is the therapy of choice to mimic a physiologic dose range and to achieve symptoms relief.

Appropriate HRT (cyclic or continuous) is useful to relieve symptoms of hypoestrogenism, and to improve the quality of life of these women, also hormonal treatment will be integrated with a healthy lifestyle [15]. The American Society for Reproductive Medicine and the International Menopause Society recommend estrogen replacement therapy for women with primary ovarian insufficiency [4, 108, 109].

Androgen treatment cannot be recommended for women with POI.

Effect on Fertility

When the FSH concentrations are greater than 12–15 mIU/mL in women who are less than the age of 40 years with regular cycles, the ovaries are unlikely to respond to the stimulating agents, such as human menopausal gonadotropins and recombinant FSH [22]. Poor ovarian response is associated with an advanced female age and a low ovarian reserve, all of which result in reduced pregnancy rates in assisted reproductive technologies (ART) [110–113]. It is important to distinguish deficient ovarian reserve (DOR) from premature ovarian insufficiency (POI) and poor ovarian responders (POR) [6].

DOR definition options include (i) woman with any of the risk factors for POR and/or (ii) an abnormal ovarian reserve test (i.e., antral follicular count (AFC) <5–7 follicles or AMH <0.5–1.1 ng/ml) [6]. DOR is characterized by poor fertility outcomes even when assisted reproductive techniques (ART) are used and represents a major challenge in reproductive medicine [6].

AMH level is correlated with the pool of primordial follicles and the number of antral follicles; both AMH and AFC are considered the most reliable and accurate markers of ovarian reserve [5, 114–119]. In the ESHRE consensus regarding POR, AMH and AFC are rather considered as post hoc test to confirm DOR after a first ovarian stimulation resulting in poor outcomes [6, 110].

Bologna ESHRE consensus 2011 defines women as “poor ovarian responders” when at least two of the following three characteristics are present:

(i) Advanced maternal age (≥40 years) or any of the risk factors for POR
(ii) A previous poor ovarian response (≤3 oocytes with a conventional stimulation protocol)

(iii) An abnormal ovarian reserve test (i.e., antral follicular count (AFC) <5–7 follicles or AMH <0.5–1.1 ng/ml) [6, 110]

According to the Bologna criteria, a low ovarian reserve is defined by an AFC of 5–7 follicles or an AMH level of 0.5–1.1 ng/ml [110]. It has recently been suggested to adjust the cutoff levels of AMH to 0.7–1.3 ng/ml [120] [113, 121].

Patients diagnosed with POI should be informed that there is a small chance of spontaneous pregnancy, but in spite of this, they should be advised to use contraception if they wish to avoid pregnancy [1]. Although the likelihood of achieving pregnancy after diagnosis is only about 5–10%, some women with POI do conceive [15, 22, 122].

Relatives of women with non-iatrogenic POI who are concerned about their risk for developing POI should be informed that:

(i) Currently there is no proved predictive test to identify women that will develop POI, unless a mutation known to be related to POI was detected.
(ii) There are no established POI preventing measures.
(iii) Fertility preservation appears as a promising option, although studies are lacking.
(iv) Their potential risk of earlier menopause should be taken into account when planning a family [1].

Serial blood sampling and transvaginal ultrasonography can demonstrate developing follicles, but disordered patterns of folliculogenesis frequently are observed, and premature luteinization is common [123]. Evidence indicates that physiologic exogenous estrogen therapy allows, but does not improve, follicular development or ovulation [124]. Although ovulation induction with exogenous gonadotropins often has been attempted, women with established hypergonadotropic hypogonadism are poor candidates. Attempts to improve ovulation rates achieved with gonadotropin therapy by pretreatment with estrogen or a GnRH agonist have met with some limited success, but pregnancy and live birth rates remain extremely low [125, 126]. POI-related infertility cannot be treated by intraconjugal-assisted reproductive techniques [6].

In the case of patients that are cancer survivors, it is important to keep in mind that in order to be autonomously fertile, a woman must have the following:

- Functioning neuroendocrine system that regulates the menstrual cycle and can maintain a pregnancy
- Healthy pool of follicles that will grow in response to hormonal cues and produce mature and fertilizable gametes
- Receptive uterus that will support embryo implantation and fetal development to term

Cancer treatments such as chemotherapy, radiotherapy, bone marrow transplantations, or surgery either in isolation or in combination can threaten fertility by compromising these three major components of the reproductive axis, by depleting woman's ovarian reserve forcing her into premature menopause, by altering the

function of the HPG axis, or by making her uterus inhospitable to an embryo [46, 127].

Preservation, surveillance, and restoration of fertility are becoming integral parts of care for women who have had cancer [39], and as important as it is to counsel patients that their fertility may be threatened by their cancer treatment, it is equally important to advise them that they may in fact never lose their fertility [46].

POI patients are infertile due to a lack of follicle growth and ovulation; the only successful fertility treatment option is in vitro fertilization (IVF) using donated oocytes [1, 22, 128]; there is no evidence that any form of treatment other than egg donation and IVF can increase the chance for pregnancy [7]. Oocyte donation pregnancies are high risk and should be managed in an appropriate obstetric unit. Antenatal aneuploidy screening should be based on the age of the donor [1].

Fertility Preservation

Driven by the increase in cancer survival rates because of advances in diagnosis and treatment of childhood, adolescent, and adult cancers, there is a greatly increased life expectancy of women diagnosed with cancer, and there is growing interest in the prevention of the loss of reproductive fitness caused either as a result of cancer or its treatment with gonadotoxic treatments [39]; efforts to preserve fertility have received significant attention [125]. Unfortunately, cancer therapies have contributed to a growing population of women with premature ovarian insufficiency [37, 129–131] . That's why counseling regarding future childbearing options will be necessary prior to initiation of chemotherapy or radiation treatment.

Established fertility preservation methods include oocyte and embryo cryopreservation, both derived from routine reproductive clinical practice, and ovarian transposition (oophoropexy), which can be offered to women undergoing pelvic irradiation. Ovarian tissue cryopreservation (OTC) is deemed experimental, needs additional informed consent, and is typically offered to patients for whom established methods cannot be applied [39, 126, 127, 132, 133]. The most suitable strategy for preserving fertility depends on various parameters including the type of cancer, the chemotherapeutic strategy, the patient's age, and the partner status [37, 127, 133–136]. According to the American Society for Reproductive Medicine, the only established method for fertility preservation is embryo cryopreservation [137]. However, cryopreservation of ovarian tissue is emerging as a promising alternative to ovarian hyperstimulation, especially in patients with prepubertal cancer, for whom ovarian hyperstimulation with subsequent oocyte or embryo cryopreservation is contraindicated, or where the time necessary to undergo ovarian stimulation is not feasible [127]. The advantages of using cryopreserved ovarian tissue include the possibility of future transplantation to temporarily restore hormonal function and fertility [127, 138].

Not all patients are candidates for or want to pursue fertility preservation; thus, patients should also be informed about alternative options for having a family after

cancer, such as oocyte donation, adoption, and choosing not to have children [37, 39, 139].

It is very important to inform women with POI that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates [122] and that when POI is established, the opportunity for fertility preservation is missed [1].

Postponement of childbearing is associated with an increased risk of infertility [140]. Women with an early age-related depletion of the ovarian reserve may be at particular risk and could thus be overrepresented among infertile patients [113].

Suzuki et al. and Kawamara et al. combined ovarian cryopreservation, fragmentation, and in vitro activation (IVA) drug treatment (the PTEN inhibitor and the PI3K activator), followed by autotransplantation, as infertility treatment for POI patients, and reported successful follicle growth and pregnancies [141, 142].

References

1. ESHRE Guideline Group on POI, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31(5):926–37.
2. Fritz M. Amenorrhea. In: Fritz MAS, Leon S, editors. Clinical gynecologic endocrinology and infertility. Philadelphia: Lippincott Williams And Wilkins; 2008. p. 436–93.
3. Lubrosky JL, Meyer P, Sowers MF, Gold EB, Santoro N. Premature menopause in a multi-ethnic population study of the menopause transition. Hum Reprod. 2002;18(1):199–206.
4. Nelson LM. Primary ovarian insufficiency. N Engl J Med. 2009;360(6):606–14.
5. Alvaro Mercadal B et al. AMH mutations with reduced in vitro bioactivity are related to premature ovarian insufficiency. Hum Reprod. 2015;30(5):1196–202.
6. Cohen J, Chabbert-Buffet N, Darai E. Diminished ovarian reserve, premature ovarian failure, poor ovarian responder-a plea for universal definitions. J Assist Reprod Genet. 2015;32(12):1709–12.
7. De Vos M, Devroey P, Fauser BCJM. Primary ovarian insufficiency. Lancet. 2010;376(9744):911–21.
8. Goswami D, Conway GS. Premature ovarian failure. Hum Reprod Update. 2005;11(4):391–410.
9. Bramble MS et al. A novel follicle-stimulating hormone receptor mutation causing primary ovarian failure: a fertility application of whole exome sequencing. Hum Reprod. 2016;31(4):905–14.
10. Simpson JL. Genetic and phenotypic heterogeneity in ovarian failure: overview of selected candidate genes. Ann N Y Acad Sci. 2008;1135:146–54.
11. Christin-Maitre S, Braham R. General mechanisms of premature ovarian failure and clinical check-up. Gynecol Obstet Fertil. 2008;36(9):857–61.
12. Persani L, Rossetti R, Cacciatore C. Genes involved in human premature ovarian failure. J Mol Endocrinol. 2010;45(5):257–79.
13. Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2015;103(3):e9–e17.
14. van der Steeg JW et al. Predictive value and clinical impact of Basal follicle-stimulating hormone in subfertile, ovulatory women. J Clin Endocrinol Metab. 2007;92(6):2163–8.
15. Luisi S et al. Premature ovarian insufficiency: from pathogenesis to clinical management. J Endocrinol Invest. 2015;38(6):597–603.

16. Gynecologists, T.A.C.o.O.a. Primary ovarian insufficiency in adolescents and young women. Obstet Gynecol. 2014;124(1):193–7.
17. Kanis JA et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24(1):23–57.
18. Bachelot A et al. Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. Eur J Endocrinol. 2009;161(1):179–87.
19. Jiao X et al. Cytogenetic analysis of 531 Chinese women with premature ovarian failure. Hum Reprod. 2012;27(7):2201–7.
20. Kalantari H et al. Cytogenetic analysis of 179 Iranian women with premature ovarian failure. Gynecol Endocrinol. 2013;29(6):588–91.
21. Rocha VB et al. Complete gonadal dysgenesis in clinical practice: the 46,XY karyotype accounts for more than one third of cases. Fertil Steril. 2011;96(6):1431–4.
22. Kovanci E, Schutt AK. Premature ovarian failure: clinical presentation and treatment. Obstet Gynecol Clin North Am. 2015;42(1):153–61.
23. Manuel M, Katayama PK, Jones Jr HW. The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. Am J Obstet Gynecol. 1976;124(3):293–300.
24. Troche V, Hernandez E. Neoplasia arising in dysgenetic gonads. Obstet Gynecol Surv. 1986;41(2):74–9.
25. Prueitt RL, Ross JL, Zinn AR. Physical mapping of nine Xq translocation breakpoints and identification of XPNPEP2 as a premature ovarian failure candidate gene. Cytogenet Cell Genet. 2000;89:44–50.
26. Davison RM, Fox M, Conway GS. Mapping of the POF1 locus and identification of putative genes for premature ovarian failure. Mol Hum Reprod. 2000;6(4):314–8.
27. Chitayat D et al. Fragile X testing in obstetrics and gynaecology in Canada. J Obstet Gynaecol Can. 2008;30(9):837–46.
28. Dal Pra C, Chen S, Furmaniak J, Smith BR, Pedini B, Moscon A, Zanchetta R. Autoantibodies to steroidogenic enzymes in patients with premature ovarian failure with and without Addison's disease. Eur J Endocrinol. 2003;148:565–70.
29. Husebye ES, Lovas K. Immunology of Addison's disease and premature ovarian failure. Endocrinol Metab Clin North Am. 2009;38(2):389–405, ix.
30. Chen S et al. Autoantibodies to steroidogenic enzymes in autoimmune polyglandular syndrome, Addison's disease, and premature ovarian failure. J Clin Endocrinol Metab. 1996;81(5):1871–6.
31. Bakalov VK et al. Selective reduction in cortical bone mineral density in turner syndrome independent of ovarian hormone deficiency. J Clin Endocrinol Metab. 2003;88(12):5717–22.
32. Bakalov VK, Vanderhoof VH, Bondy CA, Nelson LM. Adrenal antibodies detect asymptomatic auto-immune adrenal insufficiency in young women with spontaneous premature ovarian failure. Hum Reprod. 2002;17(8):2096–100.
33. Welt CK. Autoimmune oophoritis in the adolescent. Ann N Y Acad Sci. 2008;1135:118–22.
34. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489–99.
35. Goswami R et al. Prevalence of thyroid autoimmunity in sporadic idiopathic hypoparathyroidism in comparison to type 1 diabetes and premature ovarian failure. J Clin Endocrinol Metab. 2006;91(11):4256–9.
36. Kim TJ et al. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. Obstet Gynecol. 1997;89(5 Pt 1):777–9.
37. Hirshfeld-Cytron J, Gracia C, Woodruff TK. Nonmalignant diseases and treatments associated with primary ovarian failure: an expanded role for fertility preservation. J Womens Health (Larchmt). 2011;20(10):1467–77.
38. Morgan S et al. How do chemotherapeutic agents damage the ovary? Hum Reprod Update. 2012;18(5):525–35.

39. De Vos M, Smitz J, Woodruff TK. Fertility preservation in women with cancer. The Lancet. 2014;384(9950):1302–10.
40. Rosendahl M et al. Dynamics and mechanisms of chemotherapy-induced ovarian follicular depletion in women of fertile age. Fertil Steril. 2010;94(1):156–66.
41. Critchley HO. Factors of importance for implantation and problems after treatment for childhood cancer. Med Pediatr Oncol. 1999;33(1):9–14.
42. Ogilvy-Stuart AL, Shalet SM. Effect of radiation on the human reproductive system. Environ Health Perspect Suppl. 1993;101(2):109–16.
43. Wallace WH et al. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys. 2005;62(3):738–44.
44. Lo Presti A et al. Ovarian function following radiation and chemotherapy for cancer. Eur J Obstet Gynecol Reprod Biol. 2004;113(Suppl 1):S33–40.
45. Madsen BL, Giudice L, Donaldson SS. Radiation-induced premature menopause: a misconception. Int J Radiat Oncol Biol Phys. 1995;32(5):1461–4.
46. Duncan FE, Jozefik JK, Kim AM, Hirshfeld-Cytron J, Woodruff TK. The gynecologist has a unique role in providing oncofertility care to young cancer patients. PMC. 2011;6(1):24–34.
47. Bedoschi G, Turan V, Oktay K. Utility of GnRH-agonists for fertility preservation in women with operable breast cancer: is it protective? Curr Breast Cancer Rep. 2013;5(4):302–8.
48. Agha A et al. Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. J Clin Endocrinol Metab. 2005;90(12):6355–60.
49. Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF, Rubin P. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med. 1993;328(2):87–94.
50. Oktay K, Sönmezer M. Chemotherapy and amenorrhea: risks and treatment options. Curr Opin Obstet Gynecol. 2008;20:408–15.
51. Meirow D, Biederman H, Anderson RA, Hamish Wallace WH. Toxicity of chemotherapy and radiation on female reproduction. Clin Obstet Gynecol. 2010;53(4):727–39.
52. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod. 2001;7(6):535–43.
53. Brougham MF et al. Anti-Mullerian hormone is a marker of gonadotoxicity in pre- and postpubertal girls treated for cancer: a prospective study. J Clin Endocrinol Metab. 2012;97(6):2059–67.
54. Oktem O, Oktay K. Quantitative assessment of the impact of chemotherapy on ovarian follicle reserve and stromal function. Cancer. 2007;110(10):2222–9.
55. Ratcliffe MA et al. Bone mineral density (BMD) in patients with lymphoma: the effects of chemotherapy, intermittent corticosteroids and premature menopause. Hematol Oncol. 1992;10(3–4):181–7.
56. Michala L et al. Swyer syndrome: presentation and outcomes. BJOG. 2008;115(6):737–41.
57. Popat VB et al. Bone mineral density in estrogen-deficient young women. J Clin Endocrinol Metab. 2009;94(7):2277–83.
58. Freriks K et al. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. J Clin Endocrinol Metab. 2011;96(9):E1517–26.
59. Hadjidakis D, Kokkinakis E, Sfakianakis M, Raptis A. The type and time of menopause as decisive factors for bone mass changes. Eur J Clin Invest. 1999;29(10):877–85.
60. Park KH, Lee SJ, Kim JY, Kim JY, Basi SW, Kim JW. A concomitant decrease in cortical and trabecular bone mass in isolated hypogonadotropic hypogonadism and gonadal dysgenesis. Yonsei Med J. 1999;40(5):444–9.
61. Conway GS et al. Characterization of idiopathic premature ovarian failure. Fertil Steril. 1996;65(2):337–41.
62. Castaneda S et al. Reduction of bone mass in women after bone marrow transplantation. Calcif Tissue Int. 1997;60(4):343–7.

63. Han TS et al. Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. Eur J Endocrinol. 2008;159(2):179–85.
64. Bours SP et al. Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. J Clin Endocrinol Metab. 2011;96(5):1360–7.
65. Challoumas D, Cobbold C, Dimitrakakis G. Effects of calcium intake on the cardiovascular system in postmenopausal women. Atherosclerosis. 2013;231(1):1–7.
66. Prior JC, Vigna YM, Wark JD, Eyre DR, Lentle BC, Li DKB, Ebeling PR, Atley L. Premenopausal ovariectomy- related bone loss: a randomized, double-blind, one -year trial of conjugated estrogen or medroxyprogesterone acetate. J Bone Miner Res. 1997;12(11):1851–63.
67. Lindsay R et al. Prevention of spinal osteoporosis in oophorectomised women. Lancet. 1980;2(8205):1151–4.
68. Crofton PM et al. Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover. Clin Endocrinol (Oxf). 2010;73(6):707–14.
69. Stevenson M et al. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess. 2005;9(22):1–160.
70. Shapiro CL et al. Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809. Eur J Cancer. 2011;47(5):683–9.
71. Hong JS et al. Age at menopause and cause-specific mortality in South Korean women: Kanghwa Cohort Study. Maturitas. 2007;56(4):411–9.
72. Perk J et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635–701.
73. Gallagher LG et al. Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai China. Int J Epidemiol. 2011;40(6):1510–8.
74. Baba Y et al. Premature menopause is associated with increased risk of cerebral infarction in Japanese women. Menopause. 2010;17(3):506–10.
75. Kalantaridou SN et al. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. J Clin Endocrinol Metab. 2004;89(8):3907–13.
76. Lokkegaard E et al. The association between early menopause and risk of ischaemic heart disease: influence of hormone therapy. Maturitas. 2006;53(2):226–33.
77. Langrish JP et al. Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. Hypertension. 2009;53(5):805–11.
78. Ostberg JE et al. A dose-response study of hormone replacement in young hypogonadal women: effects on intima media thickness and metabolism. Clin Endocrinol (Oxf). 2007;66(4):557–64.
79. Ossewaarde ME et al. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology. 2005;16(4):556–62.
80. Amagai Y, Ishikawa S, Gotoh T, Kayaba K, Nakamura Y, Kajii E. Age at menopause and mortality in Japan: the Jichi Medical School Cohort Study. J Epidemiol. 2006;16(4):161–6.
81. Rocca WA et al. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006;7(10):821–8.
82. Wu X et al. Impact of premature ovarian failure on mortality and morbidity among Chinese women. PLoS One. 2014;9(3):e89597.
83. Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. J Psychosom Obstet Gynaecol. 2000;21(3):167–74.
84. Schmidt PJ et al. Depression in women with spontaneous 46, XX primary ovarian insufficiency. J Clin Endocrinol Metab. 2011;96(2):E278–87.

85. Boivin J. A review of psychosocial interventions in infertility. Soc Sci Med. 2003;57(12):2325–41.
86. Duijts SF et al. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. J Clin Oncol. 2012;30(33):4124–33.
87. Mann E et al. Psychosocial adjustment in women with premature menopause: a cross-sectional survey. Climacteric. 2012;15(5):481–9.
88. Mann E et al. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. Lancet Oncol. 2012;13(3):309–18.
89. Groff AA et al. Assessing the emotional needs of women with spontaneous premature ovarian failure. Fertil Steril. 2005;83(6):1734–41.
90. Orshan SA et al. The lived experience of premature ovarian failure. J Obstet Gynecol Neonatal Nurs. 2001;30(2):202–8.
91. Pacello PC et al. Dyspareunia and lubrication in premature ovarian failure using hormonal therapy and vaginal health. Climacteric. 2014;17(4):342–7.
92. Carter J et al. A cross-sectional study of the psychosexual impact of cancer-related infertility in women: third-party reproductive assistance. J Cancer Surviv. 2010;4(3):236–46.
93. Sadovsky R et al. Cancer and sexual problems. J Sex Med. 2010;7(1 Pt 2):349–73.
94. Fobair P, Spiegel D. Concerns about sexuality after breast cancer. Cancer J. 2009;15(1):19–26.
95. Carter J et al. Gynecologic cancer treatment and the impact of cancer-related infertility. Gynecol Oncol. 2005;97(1):90–5.
96. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev. 2006;(4):CD001500.
97. Le Donne M et al. The effect of vaginally administered genistein in comparison with hyaluronic acid on atrophic epithelium in postmenopause. Arch Gynecol Obstet. 2011;283(6):1319–23.
98. Grimaldi EF et al. Role of high molecular weight hyaluronic acid in postmenopausal vaginal discomfort. Minerva Ginecol. 2012;64(4):321–9.
99. Piccioni P et al. Hormonal replacement therapy after stem cell transplantation. Maturitas. 2004;49(4):327–33.
100. Madalinska JB et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol. 2006;24(22):3576–82.
101. Absolom K et al. Ovarian failure following cancer treatment: current management and quality of life. Hum Reprod. 2008;23(11):2506–12.
102. Anasti JN et al. Bone loss in young women with karyotypically normal spontaneous premature ovarian failure. Obstet Gynecol. 1998;91(1):12–5.
103. Atsma F et al. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause. 2006;13(2):265–79.
104. Furness S, et al. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev. 2012;(8):CD000402.
105. Judd HL, Legault C, Wasilauskas C, Johnson S, Merino M, Barret-Connor E, Trabal J. Effects of hormone replacement therapy on endometrial histology in postmenopausal women, The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA. 1996;275(5):370–5.
106. Benetti-Pinto CL et al. Breast density in women with premature ovarian failure using hormone therapy. Gynecol Endocrinol. 2008;24(1):40–3.
107. Soares PM, Cabello C, Magna LA, Tinois E, Laguna Benetti- Pinto C. Breast density in women with premature ovarian failure or postmenopausal women using hormone therapy: analytical cross-sectional study. Sao Paulo Med J. 2010;128(4):211–4.
108. Practice Committee of the American Society for Reproductive, Medicine. Current evaluation of amenorrhea. Fertil Steril. 2004;82(Suppl 1):S33–9.

109. Pines A et al. IMS updated recommendations on postmenopausal hormone therapy. Climacteric. 2007;10(3):181–94.
110. Ferraretti AP et al. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011;26(7):1616–24.
111. Iliodromiti S et al. The predictive accuracy of anti-Mullerian hormone for live birth after assisted conception: a systematic review and meta-analysis of the literature. Hum Reprod Update. 2014;20(4):560–70.
112. Busnelli A et al. A retrospective evaluation of prognosis and cost-effectiveness of IVF in poor responders according to the Bologna criteria. Hum Reprod. 2015;30(2):315–22.
113. Hvidman HW, et al. Infertile women below the age of 40 have similar anti-Mullerian hormone levels and antral follicle count compared with women of the same age with no history of infertility. Hum Reprod. 2016;31(5):1034–45.
114. Hansen KR et al. Correlation of ovarian reserve tests with histologically determined primordial follicle number. Fertil Steril. 2011;95(1):170–5.
115. Fleming R et al. Interpreting human follicular recruitment and antimullerian hormone concentrations throughout life. Fertil Steril. 2012;98(5):1097–102.
116. Dewailly D et al. The physiology and clinical utility of anti-Mullerian hormone in women. Hum Reprod Update. 2014;20(3):370–85.
117. dE vET A, Laven JSE, de Jong FH, Themmen APN, Fasuer BCJ. Antimullerian hormone serum levels: a putative marker for ovarian aging. Fertil Steril. 2002;77(2):357–62.
118. Broer SL et al. Anti-Mullerian hormone: ovarian reserve testing and its potential clinical implications. Hum Reprod Update. 2014;20(5):688–701.
119. Visser JA et al. Anti-Mullerian hormone: a new marker for ovarian function. Reproduction. 2006;131(1):1–9.
120. Ferraretti AP, Gianaroli L. The Bologna criteria for the definition of poor ovarian responders: is there a need for revision? Hum Reprod. 2014;29(9):1842–5.
121. La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum Reprod Update. 2014;20(1):124–40.
122. van Kasteren YM, Hundscheid RDL, Smits APT, Cremers FPM, van Zonneveld P, Braat DDM. Familial idiopathic premature ovarian failure: an overrated and uderestimated genetic disease? Hum Reprod. 1999;14(10):2455–9.
123. Nelson LM et al. Development of luteinized graafian follicles in patients with karyotypically normal spontaneous premature ovarian failure. J Clin Endocrinol Metab. 1994;79(5):1470–5.
124. Taylor AE et al. A randomized, controlled trial of estradiol replacement therapy in women with hypergonadotropic amenorrhea. J Clin Endocrinol Metab. 1996;81(10):3615–21.
125. Forman EJ, Anders CK, Behera MA. A nationwide survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. Fertil Steril. 2010;94(5):1652–6.
126. Kohler BA et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. J Natl Cancer Inst. 2015;107(6):djv048.
127. Jeruss JW, Woodruff TK. Preservation of fertility in patients with cancer. N Engl J Med. 2009;360(9):902–11.
128. Oyesanya OA et al. Prognosis of oocyte donation cycles: a prospective comparison of the in vitro fertilization-embryo transfer cycles of recipients who used shared oocytes versus those who used altruistic donors. Fertil Steril. 2009;92(3):930–6.
129. Woodruff TK. The emergence of a new interdiscipline: oncofertility. Cancer Treat Res. 2007;138:3–11.
130. Agarwal SK, Chang RJ. Fertility management for women with cancer. Cancer Treat Res. 2007;138:15–27.
131. West ER, Shea LD, Woodruff TK. Engineering the follicle microenvironment. Semin Reprod Med. 2007;25(4):287–99.

132. Riggs R et al. Does storage time influence postthaw survival and pregnancy outcome? An analysis of 11,768 cryopreserved human embryos. Fertil Steril. 2010;93(1):109–15.
133. Sonmezer MO, Oktay K. Fertility preservation in female patients. Hum Reprod. 2004;10(3):251–66.
134. Oktay K, Rodriguez-Wallberg K, Schover L. Preservation of fertility in patients with cancer. N Engl J Med. 2009;360(25):2681. author reply 2682-3.
135. Roberts JE, Oktay K. Fertility preservation: a comprehensive approach to the young woman with cancer. J Natl Cancer Inst Monogr. 2005;34:57–9.
136. Poirot C, Vacher-Lavenu MC, Helardot P, Guibert J, Brugieres L, Jouannet P. Human ovarian tissue cryopreservation: indications and feasibility. Hum Reprod. 2002;17(6):1447–52.
137. Gradishar WJ, Hellmund R. A rationale for the reinitiation of adjuvant tamoxifen therapy in women receiving fewer than 5 years of therapy. Clin Breast Cancer. 2002;2(4):282–6.
138. Pavone ME et al. Human ovarian tissue cortex surrounding benign and malignant lesions. Reprod Sci. 2014;21(5):582–9.
139. Kuwayama M et al. Highly efficient vitrification method for cryopreservation of human oocytes. Reprod Biomed Online. 2005;11(3):300–8.
140. Schmidt L et al. Demographic and medical consequences of the postponement of parenthood. Hum Reprod Update. 2012;18(1):29–43.
141. Suzuki N et al. Successful fertility preservation following ovarian tissue vitrification in patients with primary ovarian insufficiency. Hum Reprod. 2015;30(3):608–15.
142. Kawamura K, Cheng Y, Suzuki N, Deguchi M, Sato Y, Takae S, Ho C, Kawamura N, Tamura M, Hashimoto S, Sugishita Y, Marimoto Y, Hosoi Y, Yoshioka N, Ishizuka B, Hsueh A. Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. Proc Natl Acad Sci U S A. 2013;110(43):17474–9.

Chapter 12
Endometriosis

Incidence

Endometriosis is a chronic, inflammatory relatively common condition. It has an estimated prevalence of 5–10%, corresponding to about 176 million women being affected worldwide [1–3]. It is estimated to affect approximately one in ten women during their reproductive years (usually between the ages of 15 and 49) [2, 4–6].

Definition

Endometriosis is a benign disease defined by the presence of endometrial glands and stroma outside of the uterus and is associated with both pelvic pain and infertility. The ectopic endometrial tissue usually is located in the pelvis but can appear anywhere in the body [7]. The eutopic and ectopic endometrium of women with endometriosis thus differs from normal endometrium in at least three ways, exhibiting (1) high local estrogen production (estrogen-dependent disorder), (2) high local prostaglandin production, and (3) resistance to the actions of progesterone [7] (prostaglandins are responsible for pain and inflammation).

Natural History

Several pathogenic mechanisms have been proposed; not one mechanism explains all cases of endometriosis and each probably contributes, at least to some extent [7]. It is widely assumed that lesions arise through *retrograde endometrial tissue loss during menstruation*, coelomic metaplasia, and lymphatic spread in *immunologically* and *genetically* susceptible individuals. While its underlying cause is uncertain, it is

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_12

likely to be *multifactorial* including genetic factors with possible epigenetic influences, perhaps promoted through *environmental exposures* [1, 7].

Disease Presentation

Most frequent symptoms:

- Pain: most common symptom associated with endometriosis
- Dysmenorrhea
- Dyspareunia
- Non-menstrual pelvic pain
- Pain at ovulation
- Dyschezia
- Cyclic bowel or bladder symptoms
- Dysuria
- Subfertility
- Abnormal bleeding (heavy menstrual bleeding)
- Chronic fatigue
- Chronic pain syndrome [1, 3, 6–8]

Endometriosis can seriously impact on general physical, mental, and social well-being [3].

Endometriomas (benign, estrogen-dependent cyst) usually appear as smooth, dark cysts, typically associated with adhesions and containing a dense brown chocolate-like fluid [9, 10].

There is a recognized association between endometriosis and clear cell, low-grade serous, and endometrioid ovarian cancer [11], but the overall risk of ovarian cancer among women with endometriosis remains low, with a relative risk ranging from 1.3 to 1.9 which means that at worst, the lifetime risk of ovarian cancer is increased from one in 100 to two in 100 [12]. So far there is no unequivocal evidence of causality in this association. The relative risk and absolute risk of ovarian cancer among women with endometriosis are so low as not to justify routine ovarian cancer screening [1].

Diagnosis

Laparoscopy visualization with histologic examination of excised lesions (histologic evidence of ectopic endometrial glands and stroma) is the gold standard for the diagnosis of endometriosis [1, 7].

In low-resource settings, diagnosis may commence with two simple questions about pelvic–abdominal pain and infertility (accepting that a negative response does not exclude endometriosis) [1]. Physical examination has its greatest diagnostic sensitivity when performed during menstruation, but even then a normal examination does not exclude the diagnosis [13].

Recent interest has focused on endometrial immunohistochemistry for nerve fiber density [14, 15] and on urinary markers (cytokeratin 19, urinary peptide 1.8 kDa). These less invasive diagnostic tests require future formal and robust evaluation of their accuracy [1].

Classification

Laparoscopy enables endometriosis to be staged (based on its laparoscopic appearance) [1] by the revised American Society for Reproductive Medicine (r-ASRM, 1997) scoring system [16]. This classification of endometriosis is commonly used in clinical practice:

- Minimal endometriosis (stage I)
- Mild endometriosis (stage II)
- Moderate endometriosis (stage III)
- Severe endometriosis (stage IV)

The stage/extent of disease may not correlate with symptoms experienced, reproductive outcome, or recurrence risk [1, 2]. In 2009, a new staging system was proposed, called the endometriosis fertility index (EFI), link: http://www.ncbi.nlm.nih.gov/pubmed/19931076 [2].

Disease Management

There is, at present, no cure for endometriosis; treatments focus on management of symptoms [4]. Treatment for endometriosis can be expectant or limited to the use of analgesics or can involve one or a combination of medical treatments, conservative or definitive surgery, or a combination of medical and surgical treatment, depends on its clinical manifestations [7]. When the disease is less severe, medical treatment can effectively control pain in the large majority of women but has no effect on fertility. Patients must receive individualized care benefits from a multidisciplinary network of experts sufficiently skilled in providing advice on and treatment of endometriosis and its associated symptoms, based on the best available evidence, their extensive experience, and their transparent record of success rates [1].

Lifestyle and Dietary Interventions

Examples of lifestyle interventions described as helpful but not so far exposed to randomized controlled trial (RCT) include simply "talking to someone," cognitive behavioral therapy, and different types of exercise [1]. Dietary intervention following endometriosis surgery in the form of vitamins, minerals, salts, lactic ferments, and fish oil appears to be an effective alternative to hormonal treatment, that is, associated with similar pelvic pain reduction and quality-of-life improvement [1, 17].

Medical Treatment

Many clinicians support empirical medical treatment of endometriosis either prior to or without laparoscopic confirmation of endometriosis. Time to surgery may delay appropriate treatment, there is a false-negative rate in laparoscopic diagnosis, and surgery is invasive and expensive compared with empirical therapies and carries a risk of morbidity [1]. It is important to emphasize that medical therapies have no measurable effect on fertility and are not an effective treatment for patients with endometriomas or pelvic adhesions [18–20].

The World Endometriosis Society (WES) produced an international consensus statement on the current management of endometriosis in 2011 [1]; on this consensus representatives adopted as *first line* those treatments that most clinicians would consider using empirically and *second line* those treatments that most would reserve for treatment following laparoscopic diagnosis.

First-line treatment:

- *Nonsteroidal anti-inflammatory drugs (NSAIDs).*
- *Combined oral contraceptive pill (OCP)* Estrogen–progestin [21, 22] contraceptives are particularly effective in minimizing endometrioma recurrence rates after surgical removal of the cyst [23].
- *Progestins* Medroxyprogesterone acetate [24, 25] and norethisterone [22] or newer progestins such as dienogest [26–29].

Second-line medical treatment:

- Gonadotrophin-releasing hormone agonists (GnRH-a) (should be used with add-back HRT routinely).
- *Levonorgestrel-releasing intrauterine system (LNG-IUS)* [30].
- *Opioid analgesics*.
- Danazol: should not be used owing to the high-treatment burden of androgenic side effects other than for women, established on these treatments in the absence of side effects, for whom other treatments have proven ineffective. Again, acceptable side effects need to be discussed carefully with the woman [1].
- *Non-oral combined hormonal contraceptives*, such as transdermal patches and vaginal rings [31].

All women receiving medical treatment should be carefully monitored with regular follow-up consultations [1].

Complementary therapies for symptoms:

- Acupuncture
- TENS (high-frequency transcutaneous electrical nerve stimulation)

Surgical Treatment

The objectives of surgical treatment for endometriosis are to restore normal anatomical relationships, to excise or destroy all visible disease to the extent possible, and to prevent or delay recurrence [1]. For women having moderate or severe endometriosis that distorts the reproductive anatomy and hoping to restore or preserve fertility, surgery is the treatment of choice because medical treatment cannot achieve the goal; also laparoscopic surgical removal of endometriosis (through either excision or ablation of endometriosis or both) is an effective first-line approach for treating pain related to endometriosis [32, 1]. Laparoscopic surgical removal of endometriosis is recognized as being effective in improving fertility in stage I and II endometriosis [32].

It is very important to consider ovarian reserve prior to laparoscopic surgery in the woman experiencing infertility [33] in particular because evidence is growing that surgical treatment of endometriomas contributes to reduced ovarian reserve [34, 35]. Laparoscopic excision (cystectomy) whenever possible for endometriomas ≥ 4 cm in diameter improves fertility more than ablation (drainage and coagulation).

Surgery and ART should be considered as complementary strategies [1]. The best surgical approach for deep endometriosis in the context of endometriosis-related infertility remains unclear, even though observational studies suggest good fertility results in women who undergo laparoscopic excision [36, 37] or laparoscopic shaving [38].

Laparoscopic surgery for deep endometriosis, including colorectal endometriosis, should be considered a second-line treatment after failed IVF (unless IVF is not feasible or the patient has severe pain symptoms), and its place in the absence of ongoing pain symptoms needs further evaluation.

The pregnancy rate after repeat surgery is lower, approximately half of that after the first surgery [22], and two cycles of IVF might be more effective, but surgery should be considered for women with endometriosis-related infertility who continue to be symptomatic or have enlarging endometriomas and women for whom IVF is declined or repeatedly unsuccessful.

Adolescents Endometriosis treatment (both medical and surgical) for this age group may improve the quality of life, reduce symptoms, prevent more severe disease developing later, and reduce the likelihood of compromised future fertility, but further research to clarify these issues is essential [1].

Effect on Fertility

Endometriosis is strongly associated with infertility; between 20% and 40% of infertile women have the disease probably due to impaired tubo-ovarian function, distorted adnexal anatomy that inhibits or prevents ovum capture after ovulation [7]. The presence of ovarian endometrioma, chronic inflammation that impairs ovarian, tubal, or endometrial function, leading to disorders of folliculogenesis, fertilization, or implantation, possibly reduced oocyte quality [39]. The role of endometriosis in infertility is clearer where endometrial lesions have changed the pelvic anatomy (e.g., with pelvic adhesions) [4, 40, 41]. The mechanisms by which infertility occurs in women with mild disease are not well understood [41, 4].

Both endometriosis and adenomyosis (lesions occurring in the uterine–intramural–muscular layer) reduce the chance of success of assisted reproductive treatment [1, 42, 43].

While the relationship between endometriosis and infertility remains unclear, there is a strong evidence that potential or diagnosed infertility can cause considerable emotional and financial burdens for women [4, 44, 45].

Intrauterine insemination (IUI) combined with ovarian stimulation (OS) is an effective option for women with minimal-to-mild endometriosis, if the fallopian tubes are normal [46]. However, IVF is commonly offered first line in preference to IUI when endometriosis is more severe and tubal function is impaired or in the context of advanced female age and/or reduced sperm quality.

Endometriosis may have a negative impact on IVF success rates compared with other causes of infertility [42]. Nonetheless, IVF is recommended as a fertility treatment for women with endometriosis, especially if the fallopian tube function is compromised or if there are other infertility factors such as male factor [47].

Fertility Preservation

There is insufficient evidence to support routine fertility preservation for women with endometriosis [48]. Endometriosis might be an indication for fertility preservation. However, robust clinical data and cost-utility analyses are warranted prior to implementing its use in routine clinical practice [48].

Patients affected by every iatrogenic or pathologic condition known to compromise ovarian function severely have been considered as potential candidates for fertility preservation. Among them, women with endometriosis may represent a particularly suitable group since they are known to be at increased risk of infertility and earlier impairment of the ovarian reserve [22, 48, 49].

Fertility preservation may be of interest for women with endometriosis, in particular in women with bilateral unoperated endometriomas and in those who previously had excision of unilateral endometriomas and require surgery for a contralateral recurrence [48].

The evaluation should be comprehensive and should also take into consideration other factors such as a familial history of premature ovarian insufficiency, BMI, alcohol consumption, smoking, and biomarkers of ovarian reserve [50]. Considering the possible therapeutic options, egg banking should currently be preferred than ovarian cortex freezing because of the more solid available evidence [51]. The latter option should however be considered as an alternative possibility, particularly when radical surgery is envisaged [48].

References

1. Johnson NP, Hummelshoj L, World Endometriosis Society Montpellier Consortium. Consensus on current management of endometriosis. Hum Reprod. 2013;28(6):1552–68.
2. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2010;94(5):1609–15.
3. Nnoaham KE et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril. 2011;96(2):366–73. e8
4. Young K, Fisher J, Kirkman M. Endometriosis and fertility: women's accounts of healthcare. Hum Reprod. 2016;31(3):554–62.
5. Rogers PA et al. Priorities for endometriosis research: recommendations from an international consensus workshop. Reprod Sci. 2009;16(4):335–46.
6. Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am. 1997;24(2):235–58.
7. Speroff L, Glass RH, Kase NG. Endometriosis. In: Fritz MA, Speroff L, editors. Clinical gynecologic endocrinology and infertility. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 1222–48.
8. Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. Hum Reprod Update. 2011;17(3):327–46.
9. Koninckx PR et al. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril. 1991;55(4):759–65.
10. Vercellini P et al. Reliability of the visual diagnosis of ovarian endometriosis. Fertil Steril. 1991;56(6):1198–200.
11. Pearce CL et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case–control studies. Lancet Oncol. 2012;13(4):385–94.
12. Sayasneh A, Tsivos D, Crawford R. Endometriosis and ovarian cancer: a systematic review. ISRN Obstet Gynecol. 2011;2011:140310.
13. Koninckx PR et al. Diagnosis of deep endometriosis by clinical examination during menstruation and plasma CA-125 concentration. Fertil Steril. 1996;65(2):280–7.
14. Bokor A et al. Density of small diameter sensory nerve fibres in endometrium: a semi-invasive diagnostic test for minimal to mild endometriosis. Hum Reprod. 2009;24(12):3025–32.
15. Al-Jefout M et al. Diagnosis of endometriosis by detection of nerve fibres in an endometrial biopsy: a double blind study. Hum Reprod. 2009;24(12):3019–24.
16. Revised American Society for Reproductive. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril; 1997;67(5):817–21.
17. Sesti F et al. Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. Eur J Obstet Gynecol Reprod Biol. 2009;147(1):72–7.
18. Kennedy S et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005;20(10):2698–704.

19. Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vanderkerchove P. Ovularion suppression for endometriosis for women with subfertility. Cochrane Database Syst Rev. 2007;2009(3):1–56.
20. Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriosis. Hum Reprod Update. 2002;8(6):591–7.
21. Guzick DS et al. Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. Fertil Steril. 2011;95(5):1568–73.
22. Vercellini P et al. 'Waiting for Godot': a commonsense approach to the medical treatment of endometriosis. Hum Reprod. 2011;26(1):3–13.
23. Seracchioli R et al. Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. Fertil Steril. 2010;93(1):52–6.
24. Schlaff WD et al. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. Fertil Steril. 2006;85(2):314–25.
25. Crosignani P et al. Advances in the management of endometriosis: an update for clinicians. Hum Reprod Update. 2006;12(2):179–89.
26. Cosson M, Querleu D, Donnez J, Madelenat P, Koninckx, Philippe, Audebert A, Manhes H. Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study. Fertil Steril. 2002;77(4):684–92.
27. Momoeda M et al. Long-term use of dienogest for the treatment of endometriosis. J Obstet Gynaecol Res. 2009;35(6):1069–76.
28. Strowitzki T et al. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2010;151(2):193–8.
29. Petraglia F et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet. 2012;285(1):167–73.
30. Abou-Setta A, Al-Inany HG, Farquhar C. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery (Review). The Cochrane Libr. 2010;11:1–10.
31. Vercellini P et al. Post-operative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. Reprod Biomed Online. 2010;21(2):259–65.
32. Jacobson T, Duffy JMN, Barlow DH, Koninckx PR, Garry R. Laparoscopic surgery for pelvic pain associated with endometriosis (Review). Cochrane Database Syst Rev. 2009;2009(4):1–25.
33. Pellicano M et al. Ovarian endometrioma: postoperative adhesions following bipolar coagulation and suture. Fertil Steril. 2008;89(4):796–9.
34. Somigliana E et al. Surgical excision of endometriomas and ovarian reserve: a systematic review on serum antimullerian hormone level modifications. Fertil Steril. 2012;98(6):1531–8.
35. Streuli I et al. In women with endometriosis anti-Mullerian hormone levels are decreased only in those with previous endometrioma surgery. Hum Reprod. 2012;27(11):3294–303.
36. Vercellini P et al. Reproductive performance in infertile women with rectovaginal endometriosis: is surgery worthwhile? Am J Obstet Gynecol. 2006;195(5):1303–10.
37. Barri PN et al. Endometriosis-associated infertility: surgery and IVF, a comprehensive therapeutic approach. Reprod Biomed Online. 2010;21(2):179–85.
38. Donnez J et al. Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. Fertil Steril. 2010;94(1):28–32.
39. Lessey BA. Assessment of endometrial receptivity. Fertil Steril. 2011;96(3):522–9.
40. Gupta S et al. Pathogenic mechanisms in endometriosis-associated infertility. Fertil Steril. 2008;90(2):247–57.
41. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am. 2012;39(4):535–49.

42. Barnhart K. Dunsmoor-Su, Rebecca., Coutifaris, Christos, *Effect of endometriosis on in vitro fertilization*. Fertil Steril. 2002;77(6):1148–55.
43. Maubon A et al. Uterine junctional zone at magnetic resonance imaging: a predictor of in vitro fertilization implantation failure. J Obstet Gynaecol Res. 2010;36(3):611–8.
44. Fuldeore M et al. Healthcare utilization and costs in women diagnosed with endometriosis before and after diagnosis: a longitudinal analysis of claims databases. Fertil Steril. 2015;103(1):163–71.
45. Simoens S et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod. 2012;27(5):1292–9.
46. Tummon IS, Asher LJ, Martin JS, Tulandi T. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. Fertil Steril. 1997;68(1):8–12.
47. Soliman S et al. A randomized trial of in vitro fertilization versus conventional treatment for infertility. Fertil Steril. 1993;59(6):1239–44.
48. Somigliana E et al. Fertility preservation in women with endometriosis: for all, for some, for none? Hum Reprod. 2015;30(6):1280–6.
49. de Ziegler D, Barghese B. Chapron, C, *Endometriosis and infertility: pathophysiology and management*. Lancet. 2010;376:730–8.
50. Hvidman HW et al. Individual fertility assessment and pro-fertility counselling; should this be offered to women and men of reproductive age? Hum Reprod. 2015;30(1):9–15.
51. Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Reproductive, E. and Infertility. Optimizing natural fertility: a committee opinion. Fertil Steril. 2013;100(3):631–7.

Chapter 13
Uterine Fibroids

Prevalence

Uterine fibroids, also known as myomas or leiomyomas, are the most common pelvic tumor in women of reproductive age [1]. They are found in approximately 80% of hysterectomy specimens [2].

Risk Factors

Incidence rates are found to be two- to threefold greater in African American women, compared to Caucasian women [1, 3]. One study showed that estimated cumulative incidence of fibroids of any size by age 50 was greater than 80% for African American women and 70% for Caucasian women [1]. The etiology of increased incidence in African Americans is unknown.

Additional risk factors include early menarche, nulliparity [4], early exposure to oral contraceptives (one study showed 13–16 years old) [5], diet rich in red meats and alcohol, vitamin D deficiency [6], hypertension, obesity, and/or history of sexual or physical abuse [7]. Ovulation induction agents are not linked to fibroid growth [8]. Caffeine is not a risk factor, and smoking is associated with actual reduced risk due to an unknown mechanism. Several specific karyotype abnormalities have also been reported. As an example, in Caucasian women, a specific polymorphism in the transcription factor HMGA2 appears to be linked to uterine leiomyomas and shorter adult height [9].

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_13

Natural History

Uterine fibroids are benign monoclonal tumors arising from smooth muscle cells of the myometrium. They are generally associated with premenopause, as their incidence parallels the life cycle changes of the reproductive hormones estrogen and progesterone. Prospective studies have found that between 7 and 40% of fibroids regress over a period of 6 months to 3 years [10, 11]. However, there is wide variation in the growth of individual fibroids within each woman. There is further increasing evidence of postpartum regression of fibroids [12].

Most women experience shrinkage of fibroids at menopause, though postmenopausal hormone therapy may cause continued symptoms in some. Fortunately, hormone therapy does not typically lead to the development of new fibroids [13]. Symptoms are also often dependent on fibroid location and type of estrogen preparation. For example, submucosal fibroids and transdermal estrogen (in some studies) are associated with a higher risk of clinical symptoms after menopause [14, 15].

Clinical Manifestations

Symptomatic uterine fibroids generally fall under three distinct categories:

1. Heavy or prolonged menstrual bleeding (most common): thought to be secondary to abnormalities of uterine vasculature, impaired hemostasis, or molecular dysregulation of angiogenic factors [18]. Intruding submucosal and intramural fibroids are commonly associated with significant bleeding [1].
2. Pelvic pressure and pain: typically secondary to mass compression of surrounding organs of the urinary and/or GI tract. Very large uteri may further compress the inferior vena cava and increase risk of thromboembolism [19].
3. Reproductive dysfunction: distortion of the uterine cavity can result in difficulty conceiving a pregnancy, can increase risk of miscarriage, and has been associated with other pregnancy complications, such as placental abruption, fetal growth restriction, malpresentation, and preterm labor and birth [20].

Effect on Fertility

Uterine fibroids can lead to infertility in 1–2% of women [1]. Proposed mechanisms include interference with implantation, uterine distention, or contractility [20, 21].

Fibroids are often described according to their location in the uterus. Those that distort the uterine cavity are more likely to impact fertility, as well as in vitro fertilization (IVF) outcomes [21, 27]. For example, women with submucosal or intramural fibroids that protrude into the uterine cavity are found less likely to become

pregnant with increased risk of spontaneous abortion. Fibroids in other locations, such as near a fallopian tube ostium or near the cervix, may impede fertilization as well. Subserosal fibroids, in contrast, do not affect fertility outcomes [16]. In regard to IVF outcomes, one study demonstrated that having an intramural fibroid essentially halves the chance of an ongoing pregnancy following assisted conception [25, 26].

Therefore, fibroids should be ruled out in any woman presenting with infertility, and removal may become necessary prior to achievement of a pregnancy. However, it should be noted that certain fibroid treatments can subsequently impact future pregnancy. Uterine artery embolization (UAE), for example, has higher rate of miscarriage and preterm delivery, compared to myomectomy. UAE also appears to increase rate of delivery by cesarean section [22]. Thus, myomectomy is the preferred surgical therapy for women who wish to conceive. It has been shown that magnetic resonance-guided focused ultrasound surgery may also serve as a better alternative for women wishing to conceive, compared to UAE [28].

For women who are pregnant with fibroids, most do not experience fibroid-related complications [23]. Almost 90% of fibroids detected in the first trimester will regress in total fibroid volume upon reevaluation at 3–6 months postpartum [24].

References

1. Buttram Jr VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril. 1981;36(4):433.
2. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol. 1990;94(4):435–8.
3. Templeman C et al. Risk factors for surgically removed fibroids in a large cohort of teachers. Fertil Steril. 2009;92(4):1436–46.
4. Baird DD, Dunson DB. Why is parity protective for uterine fibroids? Epidemiology. 2003;14(2):247–50.
5. Marshall LM et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril. 1998;70(3):432–9.
6. Baird DD et al. Vitamin D and the risk of uterine fibroids. Epidemiology. 2013;24(3):447–53.
7. Baird D, Wise LA. Childhood abuse an fibroids. Epidemiology. 2011;22(1):15–7.
8. Stewart EA, Friedman AJ. Steroidal treatment of myomas: preoperative and long-term medical therapy. Sem Reprod Endo. 1992;10(4):344–57.
9. Hodge JC et al. Uterine leiomyomata and decreased height: a common HMGA2 predisposition allele. Hum Genet. 2009;125(3):257–63.
10. Peddada SD et al. Growth of uterine leiomyomata among premenopausal black and white women. Proc Natl Acad Sci U S A. 2008;105(50):19887–92.
11. DeWaay DJ et al. Natural history of uterine polyps and leiomyomata. Obstet Gynecol. 2002;100(1):3–7.
12. Laughlin SK et al. Pregnancy-related fibroid reduction. Fertil Steril. 2010;94(6):2421–3.
13. Yang CH et al. Effect of hormone replacement therapy on uterine fibroids in postmenopausal women—a 3-year study. Maturitas. 2002;43(1):35–9.
14. Akkad AA et al. Abnormal uterine bleeding on hormone replacement: the importance of intrauterine structural abnormalities. Obstet Gynecol. 1995;86(3):330–4.

15. Sener AB et al. The effects of hormone replacement therapy on uterine fibroids in postmenopausal women. Fertil Steril. 1996;65(2):354–7.
16. Casini ML et al. Effects of the position of fibroids on fertility. Gynecol Endocrinol. 2006;22(2):106–9.
17. Stewart EA. Uterine fibroids. Lancet. 2001;357(9252):293–8.
18. Stewart EA, Nowak RA. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. Hum Reprod Update. 1996;2(4):295–306.
19. Shiota M et al. Deep-vein thrombosis is associated with large uterine fibroids. Tohoku J Exp Med. 2011;224(2):87–9.
20. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009;91(4):1215–23.
21. Klatsky PC et al. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. Am J Obstet Gynecol. 2008;198(4):357–66.
22. Carpenter TT, Walker WJ. Pregnancy following uterine artery embolisation for symptomatic fibroids: a series of 26 completed pregnancies. BJOG Int J Obstet Gynaecol. 2005;112(3):321–5.
23. Segars JH et al. Proceedings from the Third National Institutes of Health International Congress on Advances in Uterine Leiomyoma Research: comprehensive review, conference summary and future recommendations. Hum Reprod Update. 2014;20(3):309–33.
24. Laughlin SK, Hartmann KE, Baird DD. Postpartum factors and natural fibroid regression. Am J Obstet Gynecol. 2011;204(6):496–e1.
25. Eldar-Geva T et al. Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. Fertil Steril. 1998;70(4):687–91.
26. Khalaf Y et al. The effect of small intramural uterine fibroids on the cumulative outcome of assisted conception. Hum Reprod. 2006;21(10):2640–4.
27. Hart R et al. A prospective controlled study of the effect of intramural uterine fibroids on the outcome of assisted conception. Hum Reprod. 2001;16(11):2411–7.
28. Rabinovici J et al. Pregnancy outcome after magnetic resonance–guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril. 2010;93(1):199–209.

Chapter 14
Polycystic Ovary Syndrome

Incidence

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women around the world; prevalence of PCOS varies widely depending on ethnicity, body composition, and the definition used for diagnosis [1–3, 4–8]. Literature reveals the prevalence is 15% when the broader Rotterdam criteria are applied. Prevalence may reach almost 30% in overweight and obese women [2, 4, 9, 10]. PCOS thus imposes a considerable economic burden on national health systems [11].

Definition

It is a heterogeneous disorder that affects several body systems and leads to reproductive and metabolic complications [8, 12–14]. It is also the most common cause of chronic anovulation and hyperandrogenism in young women [15].

PCOS is defined by two out of three criteria [3]:

1. Menstrual irregularity (oligo-ovulation or anovulation)
2. Hyperandrogenism (clinical or biochemical)
3. Polycystic ovarian morphology [3, 13, 16]

It is often accompanied by infertility, obesity, insulin resistance, and dyslipidemia [3, 13, 14, 17].

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_14

Natural History

PCOS is an extremely complex disorder that arises through a combination of heredity and environmental factors. PCOS ethnic variations are strongly determined by the genetic background in humans [18–20]. It is almost certainly a genetic condition [21], but the precise causes of hyperandrogenism, the cause of the change in ovarian function, and the cause of anovulation which affects a subgroup of these women remain unknown and are still under investigation [15, 21–23]. The genetic influence of PCOS was suggested in many studies, including those revealing familial clustering of PCOS and high heritability in twin studies [24–30].

Disease Presentation

PCOS is typically first identified during the early reproductive years. Ethnic origin and culture contribute to the differing manifestation of PCOS [31].

Clinical Expression Usually Includes

- Oligo or anovulation
- Hyperandrogenism (either clinical or biochemical)
- Presence of polycystic ovaries [31]

Several populations of women are at greater risk for having PCOS. These include reproductive-aged women with clinical evidence of hyperandrogenism (i.e., hirsutism, acne, or alopecia), with menstrual and/or ovulatory dysfunction, with polycystic ovaries, or with insulin resistance and metabolic abnormalities. Another potential population includes those women with overweightness or obesity [5].

These patients have an increased risk of type II diabetes [23].

Hyperandrogenism

In adult women, *clinical evidence of hyperandrogenism* includes *hirsutism, alopecia*, and *acne*; these should be considered as indicating a condition of excess androgen production [1] and the effect of androgens on the pilosebaceous unit [32].

Biochemical Hyperandrogenism Circulating androgen levels can also help to identify those hirsute women with PCOS [19]. Hyperandrogenemia should be evaluated biochemically in all women suspected of having PCOS [31]. Ideally, assessments of free testosterone (T) levels are more sensitive than the measurement of

total T for establishing the existence of androgen excess [1, 5]. Testosterone levels are elevated in most, but not all, women with PCOS.

Hirsutism

Hirsutism is the growth of excessive terminal hairs on the face or body in a male pattern [19, 33]; it is the most obvious clinical indicator of androgen excess and is an important feature of PCOS [32]. It is present in 70% of women with PCOS, and patients usually complain of cosmetically disturbing hirsutism. Typically, the onset of hirsutism in PCOS follows menarche, develops gradually, and intensifies with weight gain; substantial numbers of terminal hairs over the chin, neck, lower face, and sideburns (particularly if extending medially) indicate the presence of androgen excess. Excessive hair growth on the lower back, sternum, abdomen, shoulders, buttocks, perineal area, and inner thighs is considered abnormal [1].

Acne

The extent to which PCOS may increase risk for developing acne is therefore uncertain [32]. When acne persists after adolescence or is exacerbated in the midtwenties or midthirties, hyperandrogenemia is common, and acne may be considered a clinical sign of hyperandrogenism [1].

Alopecia

Androgenic alopecia, describing scalp hair loss in women, also can result from hyperandrogenism and is a recognized but uncommon feature of PCOS [32].

Skin and hair disorders can be both physically and psychologically very damaging.

Ovulatory and Menstrual Dysfunction

Ovulatory dysfunction represents a major clinical concern for most patients [19, 34]. As many as 85% of women with PCOS have clinical evidence of menstrual irregularities [5, 19]. The most common abnormalities are oligomenorrhea and amenorrhea; clinicians diagnose oligomenorrhea when menstrual cycles last longer than 35 days or occur less than eight times a year (during adolescence the threshold is higher and a cycle length up to 40 days may be considered normal [1]). Women

with regular menstrual cycles may have chronic anovulation [5, 19, 34]. Between one-quarter to one-third of all women with oligomenorrhea or menstrual dysfunction have PCOS [5]. Measurement of serum progesterone during the midluteal phase (days 21–22) is the best way to assess ovulation. Whereas progesterone levels >2.5 ng/mL may indicate ovulation, values ≥7 ng/mL are generally needed for regular luteal function [1].

Women with PCOS may ovulate spontaneously; how frequently this occurs is unknown [35], but ovulations have been reported in up to 32% of "cycles" [31]. Amenorrheic women with PCOS usually have the most severe hyperandrogenism and higher antral follicle counts when compared with women presenting with oligomenorrhea or regular menstrual cycles [31].

Women with PCOS have an increased proportion of primordial follicles and a corresponding increase in activated growing (primary) follicles [36, 37]. Small follicles do not develop into ovulatory follicles (growth of these follicles is arrested before they mature [38]) and also have a reduced rate of apoptosis compared with those in a normal ovary [39]; this gives rise to the typical morphology of a polycystic ovary, a so-called stockpiling effect [40]. In PCOS there is an abnormal follicular development and apparent failure to select a dominant follicle results in anovulation [41].

PCOS is characterized by an increased number of follicles at all growing stages [49–51]. This increase is particularly seen in the pre-antral and small antral follicles, those which primarily produce AMH [52, 53]. Thus, elevated serum AMH level, as a reflection of the stock of pre-antral and small antral follicles, is two- to fourfold higher in women with PCOS than in healthy women [54–57] and is found in all PCOS populations [21, 22, 42–44].

AMH is an indicator of ovarian reserve and follicle growth. There is actually a very good correlation between serum AMH levels and ultrasonographic measure of the antral follicular count (AFC) [23, 24]. This can be explained because circulating AMH is mostly produced by granulosa cells of follicles from 2 to 9 mm in diameter (60%), and those small follicles are precisely the ones counted on the ultrasound when the AFC is done [15, 25].

Measurement of serum AMH is even more sensitive and specific than the AFC as it also reflects pre-antral and small antral follicles (<2 mm), which are hardly seen in ultrasound. Serum AMH is therefore a deeper "probe" for the growing follicular pool than the AFC [6, 15]. The strength of this relationship is even greater with newer ultrasound technology allowing the counting of 1–2-mm follicles [23, 45]. Elevated AMH values (>4.5 ng/mL) may be useful as a substitute for ovarian morphology when no accurate ovarian ultrasound is available [45]. Serum AMH level is also correlated to the severity of PCOS symptoms [68] and is higher when hyperandrogenism [62, 80] or oligo-anovulation is present [15, 25, 43, 46, 47]. Evidence supports the hypothesis that the high AMH concentrations present in women with PCOS play an integral role in causing anovulation due to its inhibitory influence on the actions of FSH that normally promotes follicular development from the small antral stage to ovulation [40]. It is now undeniable that serum AMH is a valuable tool for the diagnosis of PCOS [15].

Polycystic Ovaries

Approximately 75% of anovulatory women have multicystic or polycystic ovaries [32]. The density of pre-antral and small antral follicles in the polycystic ovary is six times that of the normal ovary [36, 40].

In 2003, Rotterdam PCOS criteria updated the definition of PCO as the presence of 12 or more follicles (AFC) in each ovary measuring 2–9 mm in diameter and/or an increased ovarian volume (10 mL) in at least one ovary [19, 48–50]. These criteria were based on a completely different ultrasound technology with new ultrasound; these criteria are no longer appropriate in the clinic [51]. New AES guidelines, which are based upon a review of the data published using new ultrasound technology, have increased the threshold count of small ovarian follicles to 25 [22]. Ovarian size threshold has not been influenced by new technologies, and 10 mL remains the threshold between normal and increased ovary size [52].

Polycystic ovaries result from chronic anovulation that persists for a sufficient length of time [32]. This morphology is commonly found in normal women [19, 51]. Polycystic ovaries are observed in 20–30% of the population and the prevalence in general population appears to decrease with age [52]; it may be estimated that about 20% of women with polycystic ovaries have PCOS [5]; even 14% of women using oral contraceptives also meet the ultrasonographic criteria for polycystic ovaries. Moreover, polycystic ovaries are commonly observed during normal pubertal development [53].

Ovarian morphology must be assessed by transvaginal ultrasound. Transabdominal ultrasound is a less accurate technique, but it is still a possibility in special situations [1].

Other Features of the Polycystic Ovary Syndrome

PCOS has other common features besides hyperandrogenism and ovulatory dysfunction that are not included in any diagnostic criteria, including abnormal patterns of gonadotropin secretion, insulin resistance, and related metabolic abnormalities, such as dyslipidemia [32].

Abnormal Gonadotropin Secretion

Devoted to the pathophysiology of the disorder, increased serum LH concentrations, low normal FSH levels, and increased LH/FSH ratios are typical. Gonadotropin levels or ratios are not a reliable diagnostic criterion; they neither make nor exclude the diagnosis [32].

Insulin Resistance

PCOS is associated with increased risk of impaired glucose tolerance (IGT), gestational diabetes mellitus (GDM), and type 2 diabetes (T2D) [30, 31, 54, 55]. Insulin resistance and compensatory hyperinsulinemia are common but not universal features of women with PCOS [32]. The overall prevalence of insulin resistance among women with PCOS is between 50% and 75%, and greater in obese than in lean women with PCOS [31, 32].

Risk of IGT or diabetes is highest in women who have both oligo/anovulation and hyperandrogenism [31, 56]. All women with PCOS should therefore be screened with an oral glucose tolerance test at the time of presentation. Evaluation also should include blood pressure, waist circumference, and a lipid profile, to help identify those with features of the metabolic syndrome [32].

Dyslipidemia

Dyslipidemia is perhaps the most common metabolic abnormality observed in women with PCOS. Applying the National Cholesterol Education Program guidelines, nearly 70% have at least one borderline or elevated lipid level [32]. Insulin resistance and hyperinsulinemia are associated with decreased high-density lipoprotein (HDL) cholesterol and elevated triglyceride levels, and numerous studies have observed such abnormalities in women with PCOS [32]. Triglyceride, low-density lipoprotein (LDL), and non-high-density lipoprotein (HDL) cholesterol changes are higher compared with non-PCOS women [31].

Assessing waist circumference and non-HDL cholesterol appear to be the most useful clinical indicators of this metabolic disturbance. Genetic, environmental, and hormonal factors coexist to regulate lipid metabolism in women with PCOS, which is not fully explained by body weight alone.

Obesity

Obesity is a common feature of PCOS; many women with PCOS are overweight or obese [19, 57–59].

There is widespread variability in the prevalence of overweight (BMI 25–30 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2) women in PCOS populations across different countries [31]; the prevalence of obesity is approximately 50% overall [32].

Obesity is associated with PCOS, but its causal role has yet to be determined; explanations include reverse causality (i.e., PCOS increases susceptibility to weight gain) and synergistic but independent roles for obesity and PCOS in infertility [16]. PCOS women are more likely to have upper body fat distribution.

Greater abdominal or visceral adiposity is associated with greater IR, which could exacerbate the reproductive and metabolic abnormalities in PCOS [31, 60].

Metabolic Abnormalities and Associated Health Risks

The increased metabolic risk might be related to obesity as well as to genetic and environmental factors [61, 62]. Metabolic disorders are often associated to PCOS (up to 50%), including an increased rate of insulin resistance, regardless of obesity [63].

The MetS is accepted as a cardiovascular risk factor and requires three of the following five clinical characteristics: elevated waist circumference (population specific, >88 cm in the United States), systolic and/or diastolic blood pressure (≥130 mm Hg systolic; ≥85 mm Hg diastolic), fasting blood glucose (≥100 mg/dL) or previously established diabetes mellitus, fasting serum triglycerides (≥150 mg/dL), and decreased serum high-density lipoprotein cholesterol levels (<50 mg/dL) [19].

Many women with PCOS have some degree of dyslipidemia. Many also have central obesity, and some even meet criteria for the diagnosis of the metabolic syndrome. Metabolic dysfunction in women with PCOS leads to exaggerated risk for CVD with aging [31]. The more severe PCOS phenotypes are associated with greater magnitude of CVD risk, and this has been found in obese and nonobese women [64, 65].

Effect on Mental Health

The prevalence of behavioral disorders, depression, and anxiety is higher in women with PCOS than in the general population. Such mood disorders, capable of impairing quality of life, can be prominent in adolescents faced with issues of self-presentation, in young adult women concerned with fertility, and in women of all ages with respect to eating, overweight, and clinical manifestations of androgen excess [19, 31, 65–69].

Cancer Risks

Women with PCOS have multiple risk factors for endometrial cancer that include obesity, metabolic abnormalities (such as diabetes, hyperinsulinemia, hypertension, and obesity), and history of oligomenorrhea with prolonged exposure to unopposed estrogen (chronic anovulation). Studies have noted a 2.7-fold increased risk for developing endometrial cancer versus the general population [19, 70, 71].

Presumably, the mechanism relates to constant, unrelenting estrogen stimulation of the endometrium, predisposing to abnormal patterns of growth. Endometrial hyperplasia and even endometrial cancer can be encountered in young anovulatory women [32, 72]. Consequently, for those with long-standing anovulation, endometrial sampling to exclude endometrial hyperplasia is a prudent precaution. The decision on whether to perform an endometrial biopsy should not be based on the patient's age but on the duration of potential exposure to unopposed estrogen stimulation.

Studies regarding PCOS and ovarian cancer risk are contradictory [19].

Effect on Fertility

PCOS is the commonest cause of anovulatory infertility and eugonadotropic hypogonadism according to the World Health Organization [8, 73], and it is often diagnosed for the first time in the fertility clinic [40]. Infertility is the main clinical implication of ovulatory dysfunction in PCOS [1]. Seventy-five percent of these women suffer infertility due to anovulation. This may be explained by the effects of obesity, metabolic, inflammatory, and endocrine abnormalities on ovulatory function, oocyte quality, and endometrial receptivity. Ovarian hyperandrogenism and hyperinsulinemia may promote premature granulosa cell luteinization, and paracrine dysregulation of growth factors may disrupt the intrafollicular environment and impair cytoplasmic and/or nuclear maturation of oocytes [74]. These features are not universal, and oocyte quality, fertilization, and implantation rates in an individual woman with PCOS can be normal [14, 31, 75].

Pathophysiology

Phenotypic heterogeneity between cases has limited the ability to make definitive conclusions regarding its etiology and pathophysiology [16]; the pathophysiology of PCOS is complex and reflects the interactions between genetic, metabolic, fetal, and environmental factors [19]. Among these factors, disordered gonadotropin secretion, HA, insulin resistance and hyperinsulinemia, ovarian dysfunction, and follicular arrest are prominent [19]. The hyperandrogenism and anovulation that accompany PCOS may be caused by abnormality in four endocrinologically active compartments: (1) the ovaries, (2) the adrenal glands, (3) the peripheral fat, and (4) the hypothalamus–pituitary compartment. The insulin resistance results in a compensatory hyperinsulinemia, which augments LH-stimulated androgen production in an ovary genetically predisposed to PCOS. Arrest of follicular development and anovulation could be caused by the abnormal secretion of gonadotrophins, intraovarian androgen excess, direct effect of insulin, or a combination of these factors [76].

Diagnosis

Diagnosis of polycystic ovary syndrome is based primarily on the clinical history and physical examination. The major clinical features of polycystic ovary syndrome are hyperandrogenism and menstrual dysfunction [32]. It is generally accepted that PCOS is not a specific endocrine disease but a syndrome represented by a collection of signs and symptoms and that no one sign, symptom, or test is diagnostic. Establishing criteria for diagnosis of PCOS has proven both challenging and controversial [32]. The diagnostic criteria for PCOS are based on expert consensus, not evidence. In 2003, the Rotterdam consensus expanded the diagnostic criteria to include at least two of the following features:

1. Clinical or biochemical hyperandrogenism
2. Oligo-anovulation (cycle disorder)
3. Polycystic ovaries (PCO) (antral follicular excess on ultrasound with ≥12 follicles from 2 to 9 mm per ovary and/or ovarian volume ≥10 ml) [1]

An Expert Panel from the 2012 NIH Evidence-Based Methodology Workshop on PCOS recommended that clinicians use the more recent Rotterdam criteria for diagnosis [19, 49].

The consensus opinion has generally agreed that the ovary is central to the disorder and that it is necessary to exclude other endocrinological disorders before making the diagnosis (PCOS is a diagnosis of exclusion). These disorders include nonclassic adrenal hyperplasia, Cushing's syndrome, androgen-producing tumors, and drug-induced androgen excess. In addition, clinicians should rule out ovulatory dysfunction from other causes, including thyroid dysfunction and hyperprolactinemia, as well as pregnancy in reproductive-aged women [19].

Evaluation of women with suspected polycystic ovary syndrome should include:

- Serum thyroid-stimulating hormone (TSH)
- Serum prolactin
- 2 h oral glucose tolerance test
- Fasting lipid profile
- Endometrial sampling (in women whose history indicates potential long-term exposure to unopposed estrogen stimulation)
- Serum testosterone (in women with moderate or severe hirsutism)
- Morning follicular phase serum 17-hydroxyprogesterone (in women with a pre- or perimenarcheal onset of hirsutism, a family history of congenital adrenal hyperplasia, or high-risk ethnicity)
- Overnight dexamethasone suppression test (in women with signs or symptoms of hypercortisolism) [32]

Improved and standardized androgen assays, novel methods for documenting chronic anovulation that go beyond menstrual history, and imaging technology may refine the diagnostic criteria [19].

Diagnosis in Adolescents

PCOS commonly presents during adolescence. Criteria for the diagnosis of PCOS in adolescents differ from those used for older women of reproductive age because the signs and symptoms are heterogeneous in adolescents and may vary over time [1]. Ovarian dysfunction in adolescents should be based on oligomenorrhea and/or biochemical evidence of oligo/anovulation. Ultrasound is not a first-line investigation in women <17 years of age. Multifollicular ovaries can be a normal stage of development in adolescence and early adulthood [19, 51]. Enlarged ovarian size (≥10 mL) may be a simpler indicator of adult PCOS than follicular number in adolescent girls who have hyperandrogenism and oligomenorrhea for at least 2 years postmenarche [19, 77]. During adolescence, therefore, only hirsutism should be considered a substitute of biochemical hyperandrogenism [1, 77]. Acne is very common and often reversible, whereas alopecia is uncommon and generally has other causes.

Adolescence is a crucial time for diagnosis because this is a time frame when many patients with PCOS start gaining weight. Adolescents should therefore be followed carefully to confirm the diagnosis and reduce the frequency of later complications in the CV system and type 2 diabetes mellitus [1]; the diagnosis may lead to greater recognition of metabolic risk factors, with earlier intervention preventing sequelae [78, 79]. It is also important to treat psychologic and dermatologic Issues. Groups at risk (e.g., obese, hirsute, irregular menses) should be identified but be cautious of overdiagnosing PCOS [31].

Disease Management

The management of women with PCOS should seek to correct or prevent both its immediate and longer-term clinical consequences, which may include all of the following:

- Menstrual abnormalities
- Increased risk for developing endometrial hyperplasia and neoplasia
- Hyperandrogenism (hirsutism, acne, alopecia)
- Infertility
- Increased risk for developing type 2 diabetes
- Increased risk for developing cardiovascular disease

Women with PCOS who do not desire pregnancy need contraception. No contraceptive methods are contraindicated in PCOS. However, some of the features associated with PCOS (obesity, insulin resistance, etc.) may represent a relative contraindication to the use of combined OCPs. OCPs suppress LH secretion and lead to a decrease in ovarian androgen production. The estrogenic component increases the levels of SHBG, which, in turn, results in a decrease in circulating

free T levels [31]. The benefits of OCPs outweigh the risks in most patients with PCOS [31].

Those seeking to conceive are candidates for ovulation induction.

The important point to emphasize is that women with chronic anovulation require comprehensive clinical management that addresses their immediate needs but also considers their longer-term health and incorporates appropriate risk reduction strategies [32].

Lifestyle and Dietary Interventions

In many cases, lifestyle changes will be an important part of the clinical management, requiring careful education, counseling, encouragement, and follow-up. These changes included changes in diet, exercise, and/or behaviors that benefit general health, including weight loss and weight gain prevention [19, 80]. There is general consensus that weight and glycemic parameters are improved [19]. A few randomized controlled studies on lifestyle interventions exist, and these suggest substantial reproductive and metabolic benefit [28, 31].

Management of Menstrual Abnormalities

Estrogen–progestin contraceptives are the most common treatment for the menstrual abnormalities associated with chronic anovulation because they induce regular cyclic menses and attenuate endometrial growth, thereby preventing dysfunctional uterine bleeding and also eliminating the risk for developing endometrial hyperplasia and neoplasia. Cycle control is usually achieved by the use of OCPs in women with PCOS [31]. In those who refuse or have a contraindication to the use of estrogen–progestin contraceptives, the same can be achieved with cyclic or continuous treatment with progestins alone. However, progestin treatment forfeits some of the other important actions of estrogen–progestin contraceptives that help in the treatment of hyperandrogenism.

Knowing and understanding the health implications and consequences of chronic anovulation and methods for their effective management are far more important than assigning a specific diagnosis of PCOS.

Management of Hyperandrogenism

Mild focal hirsutism can be managed effectively with cosmetic measures (shaving, plucking, waxing, depilatories), but most who present with a complaint of hirsutism are already using one or more such methods and will require treatment. Medical management options include primarily estrogen–progestin contraceptives and antiandrogens (e.g., spironolactone) [32]. Antiandrogens are effective for the treatment of hirsutism but should be used in combination with an estrogen–progestin contraceptive or another highly reliable method (e.g., an intrauterine device) because of their potential to adversely affect sexual development in a male fetus if the patient were to conceive unexpectedly. Prolonged (6 months) medical therapy for hirsutism is necessary to document effectiveness. No effective treatment for alopecia is known [1, 31, 81–86, 95, 96].

Management of Women at Risk for T2D

First-Line Treatment
- Diet and lifestyle modifications

Second-Line Treatment
- Metformin treatment is indicated in those with IGT who do not respond adequately to calorie restriction and lifestyle changes. In those with frank diabetes, metformin is safe and effective, whereas there is concern about the use of thiazolidinediones and glucagon-like peptide-1 analogs in women of reproductive age [31, 87]. Cellular and molecular mechanisms of insulin resistance in PCOS differ from those in other common insulin-resistant states such as obesity and diabetes. Consequently, the role of insulin sensitization therapy in PCOS remains limited to the prevention of cardiovascular disease and type 2 diabetes (T2D) [16, 88, 89]. Metformin is a biguanide oral insulin-sensitizing agent and currently is the most widely used drug in the world for the treatment of type 2 diabetes mellitus. The most logical candidates for treatment with metformin are women with impaired glucose tolerance or diabetes, those with obvious evidence of severe insulin resistance and women having other features of the metabolic syndrome, such as central obesity, hypertension, and dyslipidemia.

Preconceptional Issues and Infertility Treatment

Assessment of a woman with PCOS for infertility involves evaluating for preconceptional issues that may affect response to therapy or lead to adverse pregnancy outcomes and evaluating the couple for other common infertility issues.

When pregnancy occurs in women with PCOS, there is a higher incidence of GDM (40–50%) and associated fetal macrosomia, gestational hypertensive disorders (such as preeclampsia and pregnancy-induced hypertension) (5%), and birth of small-for-gestational-age babies (10–15%) [55]. Women should be screened and treated for hypertension and diabetes and should be counseled about weight loss prior to attempting conception.

First-Line Treatment
- Lifestyle modification (associated with improved endocrine profile)
- Clomiphene citrate
- Letrozole (aromatase inhibitor) [1, 90]

Clomiphene Citrate (CC) First-line pharmacologic therapy for ovulation induction (OI) blocks estrogen receptors at the level of the hypothalamus [90].

Letrozole It blocks the conversion of androgens to estrogens in the ovary. This decrease in estrogen levels provides negative feedback in the hypothalamus, which

stimulates the pituitary gland to secrete follicle-stimulating hormone. The FDA has not approved aromatase inhibitors for ovulation induction [90].

Second-Line Medical Treatment (For Women CC Resistant) Combined treatment with CC and metformin
- Recombinant FSH
- Laparoscopic ovarian drilling (LOD)

Combined Treatment with CC and Metformin
Metformin has been used for OI either as first-line therapy, second-line therapy, or in combination with CC. Many studies have been carried out to evaluate the effects of metformin in patients with PCOS; however, most were observational [76]. Although metformin was associated with improved ovulation and clinical pregnancy rates, it did not improve live birth rates whether prescribed alone or in combination with clomiphene citrate [91, 92]. Currently, the US Food and Drug Administration (FDA) have not approved metformin for the treatment of PCOS. Theoretically, however, metformin improves insulin sensitivity, which can decrease androgen levels and restore ovulatory and menstrual function [93]. Approximately 20–30% of women do not ovulate while taking clomiphene citrate. For this group the addition of metformin may be beneficial [94].

Recombinant FSH Induction of ovulation with exogenous gonadotropins is highly effective but requires careful monitoring to avoid the intrinsic risks of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). AMH determination may be a helpful tool in the prediction of the ovarian response to gonadotropins in PCOS. Difficulties persist, however, since there is no consensus on the threshold for the AMH values [15].

Laparoscopic Ovarian Drilling (LOD) The aim of this procedure is to trigger spontaneous ovulation by destroying small amounts of ovarian cortex drilling significantly altering the hormonal environment within the ovary [15]. There is some risk for causing postoperative adnexal adhesions and decreased ovarian reserve [32].

Third-Line Treatment
In many cases of PCOS, the safest and most effective means of achieving pregnancy is through assisted reproductive technologies such as in vitro fertilization [85, 86, 90, 95].

The optimal protocol for women with PCOS who failed to conceive after controlled ovarian stimulation has not yet been defined [84]. The aim is to determine the preferred protocol for PCOS patients with a high LH/FSH ratio—IVF with GnRH long agonist, antagonist, or in vitro maturation (IVM) [84].

IVM is a more patient-friendly treatment and involves maturation of immature oocytes in the laboratory thus minimizing gonadotrophin stimulation. It can eliminate the risk of OHSS and should be highly recommended as a treatment option particularly for women with PCO who are at an increased risk of the significant morbidity resulting from OHSS after standard IVF treatment [81, 83]. A modified IVM protocol recently demonstrated clinical pregnancy success rates as high as

44.7% for patients with PCOS [82]. Similar success rates were achieved when using this protocol to compare IVF and intracytoplasmic sperm injection (ICSI) fertilization techniques in IVM [81, 96].

If uterine dyssynchrony occurs or if other reasons such as ovarian hyperstimulation prevent embryo transfer, the embryos can be frozen (cryopreserved) and transferred in a subsequent frozen embryo transfer cycle. Successful cryopreservation techniques have dramatically reduced the risk of hyperstimulation, and use of single-embryo transfer has reduced multiple gestations and births [76, 90].

Further research is necessary to optimize protocols and laboratory aspects of IVM [76].

Fertility Preservation

Transfer of frozen-thawed IVM oocytes during an artificial cycle in PCOS patients is feasible and leads to pregnancy and live birth [98].

References

1. Goodman NF et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and Pcos Society Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome - Part 1. Endocr Pract. 2015;21(11):1291–300.
2. Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab. 2000;85(7):2434–8.
3. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41–7.
4. Azziz R et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456–88.
5. Li R et al. Prevalence of polycystic ovary syndrome in women in China: a large community-based study. Hum Reprod. 2013;28(9):2562–9.
6. Wang S, Alvero R. Racial and ethnic differences in physiology and clinical symptoms of polycystic ovary syndrome. Semin Reprod Med. 2013;31(5):365–9.
7. Kollmann M et al. Maternal and neonatal outcomes in pregnant women with PCOS: comparison of different diagnostic definitions. Hum Reprod. 2015;30(10):2396–403.
8. Apridonidze T et al. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90(4):1929–35.
9. March WA et al. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. 2010;25(2):544–51.
10. Azziz R et al. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrinol Metab. 2005;90(8):4650–8.
11. Wild RA. Long-term health consequences of POCS. Hum Reprod Update. 2002;8(3):231–41.
12. Norman RJ et al. Polycystic ovary syndrome. The Lancet. 2007;370(9588):685–97.

13. Fauser BC et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97(1):28–38. e25.
14. Dumont A et al. Role of Anti-Mullerian hormone in pathophysiology, diagnosis and treatment of polycystic ovary syndrome: a review. Reprod Biol Endocrinol. 2015;13(1):137.
15. Day FR et al. Causal mechanisms and balancing selection inferred from genetic associations with polycystic ovary syndrome. Nat Commun. 2015;6:8464.
16. de Wilde MA et al. Insulin action in women with polycystic ovary syndrome and its relation to gestational diabetes. Hum Reprod. 2015;30(6):1447–53.
17. Corbett S, Morin-Papunen L. The polycystic ovary syndrome and recent human evolution. Mol Cell Endocrinol. 2013;373(1–2):39–50.
18. Dumesic DA et al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev. 2015;36(5):487–525.
19. Casarini L, Brigante G. The polycystic ovary syndrome evolutionary paradox: a genome-wide association studies-based, in silico, evolutionary explanation. J Clin Endocrinol Metab. 2014;99(11):E2412–20.
20. Kosova G, Urbanek M. Genetics of the polycystic ovary syndrome. Mol Cell Endocrinol. 2013;373(1–2):29–38.
21. Cui L et al. Polycystic ovary syndrome susceptibility single nucleotide polymorphisms in women with a single PCOS clinical feature. Hum Reprod. 2015;30(3):732–6.
22. Dewailly D et al. The physiology and clinical utility of anti-Mullerian hormone in women. Hum Reprod Update. 2014;20(3):370–85.
23. Vink JM et al. Heritability of polycystic ovary syndrome in a Dutch twin-family study. J Clin Endocrinol Metab. 2006;91(6):2100–4.
24. Lee H et al. A genetic risk score is associated with polycystic ovary syndrome-related traits. Hum Reprod. 2016;31(1):209–15.
25. Legro RS, Driscoll D, Strauss JF, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci U S A. 1998;95:14956–60.
26. Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. Fertil Steril. 2010;93(7):2421–3.
27. Moran LJ et al. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16(4):347–63.
28. Moran LJ et al. Psychological parameters in the reproductive phenotypes of polycystic ovary syndrome. Hum Reprod. 2012;27(7):2082–8.
29. Moran L et al. Polycystic ovary syndrome: a biopsychosocial understanding in young women to improve knowledge and treatment options. J Psychosom Obstet Gynaecol. 2010;31(1):24–31.
30. Consensus on women's health aspects of polycystic ovary syndrome (PCOS) Amsterdam Eshre Asrm-Sponsored 3rd Pcos Consensus Workshop Group. Hum Reprod. 2012;27(1):14–24.
31. Speroff L. Chronic anovulation and the polycystic ovary syndrome. In: Fritz MA, Speroff L, editors. Clinical gynecologic endocrinology and infertility: Lippinicott; 2008. p. 496–531.
32. Escobar-Morreale HF et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update. 2012;18(2):146–70.
33. Broekmans FJ et al. PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG. 2006;113(10):1210–7.
34. Laven JS, Imani B, Eijkemans MJC, Fauser BCJ. New approach to polycystic ovary syndrome and other forms of anovulatory infertility. Obstet Gynecol Surv. 2002;57(11):755–67.
35. Webber LJ et al. Formation and early development of follicles in the polycystic ovary. Lancet. 2003;362(9389):1017–21.
36. Maciel GA et al. Stockpiling of transitional and classic primary follicles in ovaries of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2004;89(11):5321–7.

37. Jonard S, Dewailly D. The follicular excess in polycystic ovaries, due to intra-ovarian hyperandrogenism, may be the main culprit for the follicular arrest. Hum Reprod Update. 2004;10(2):101–17.
38. Beloosesky R et al. Induction of polycystic ovary by testosterone in immature female rats: modulation of apoptosis and attenuation of glucose/insulin ratio. Int J Mol Med. 2004;14(2):207–15.
39. Homburg R, Crawford G. The role of AMH in anovulation associated with PCOS: a hypothesis. Hum Reprod. 2014;29(6):1117–21.
40. Franks S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. Hum Reprod Update. 2008;14(4):367–78.
41. Pigny P et al. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. J Clin Endocrinol Metab. 2003;88(12):5957–62.
42. Laven JS et al. Anti-Mullerian hormone serum concentrations in normoovulatory and anovulatory women of reproductive age. J Clin Endocrinol Metab. 2004;89(1):318–23.
43. Park AS et al. Serum anti-mullerian hormone concentrations are elevated in oligomenorrheic girls without evidence of hyperandrogenism. J Clin Endocrinol Metab. 2010;95(4):1786–92.
44. Dewailly D et al. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries. Hum Reprod. 2011;26(11):3123–9.
45. Pellatt L et al. Granulosa cell production of anti-Mullerian hormone is increased in polycystic ovaries. J Clin Endocrinol Metab. 2007;92(1):240–5.
46. Catteau-Jonard S et al. Polycystic ovaries at ultrasound: normal variant or silent polycystic ovary syndrome? Ultrasound Obstet Gynecol. 2012;40(2):223–9.
47. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. Hum Reprod Update. 2003;9(6):505–14.
48. Group, G.W. Education and debate. BMJ. 2004;328:1–8.
49. Jonard S, Robert Y, Cortet-Rudelli C, Pigny P, Decanter C, Dewailly D. Ultrasound examination of polycystic ovaries: is it worth counting the follicles? Hum Reprod. 2003;18(3):598–603.
50. Johnstone EB et al. The polycystic ovary post-rotterdam: a common, age-dependent finding in ovulatory women without metabolic significance. J Clin Endocrinol Metab. 2010;95(11):4965–72.
51. Koivunen R, Laatikainen T, Tomas C, Huhtaniemi I, Tapanainen J, Martikainen H. The prevalence of polycystic ovaries in healthy women. Acta Obstet Gynecol Scand. 1999;78:137–41.
52. Polson DW et al. Polycystic ovaries-a common finding in normal women. Lancet. 1988;1(8590):870–2.
53. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997;18(6):774–800.
54. Boomsma CM et al. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update. 2006;12(6):673–83.
55. Barber TM et al. Metabolic characteristics of women with polycystic ovaries and oligo-amenorrhoea but normal androgen levels: implications for the management of polycystic ovary syndrome. Clin Endocrinol (Oxf). 2007;66(4):513–7.
56. Diamanti-Kandarakis E. Role of obesity and adiposity in polycystic ovary syndrome. Int J Obes (Lond). 2007;31(Suppl 2):S8–13. ; discussion S31-2.
57. Hoeger KM, Oberfield SE. Do women with PCOS have a unique predisposition to obesity? Fertil Steril. 2012;97(1):13–7.
58. Legro RS. Obesity and PCOS: implications for diagnosis and treatment. Semin Reprod Med. 2012;30(6):496–506.
59. Lord J et al. The central issue? Visceral fat mass is a good marker of insulin resistance and metabolic disturbance in women with polycystic ovary syndrome. BJOG. 2006;113(10):1203–9.
60. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med. 2005;352:1223–36.

61. Ehrmann DA et al. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91(1):48–53.
62. Dunaif A et al. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989;38(9):1165–74.
63. Zhao X et al. Association of biochemical hyperandrogenism with type 2 diabetes and obesity in Chinese women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2010;108(2):148–51.
64. Dokras A, CliftonS, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome a systematic review and meta-analysis. Obstet Gynecol. 2011;117(1):145–52.
65. de Niet JE et al. Psychological well-being and sexarche in women with polycystic ovary syndrome. Hum Reprod. 2010;25(6):1497–503.
66. Himelein MJ, Thatcher SS. Polycystic ovary syndrome and mental health: a review. Obstet Gynecol Surv. 2006;61(11):723–32.
67. Elsenbruch S et al. Quality of life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88(12):5801–7.
68. Jones GL et al. Health-related quality of life measurement in women with polycystic ovary syndrome: a systematic review. Hum Reprod Update. 2008;14(1):15–25.
69. Haoula Z, Salman M, Atiomo W. Evaluating the association between endometrial cancer and polycystic ovary syndrome. Hum Reprod. 2012;27(5):1327–31.
70. Chittenden B. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed Online. 2009;19(3):398–405.
71. Dumesic DA, Lobo RA. Cancer risk and PCOS. Steroids. 2013;78(8):782–5.
72. Group, E.C.W. Health and fertility in World Health Organization group 2 anovulatory women. Hum Reprod Update. 2012;18(5):586–99.
73. Dumesic DA, Padmanabhan V, Abbott DH. Polycystic ovary syndrome and oocyte developmental competence. Obstet Gynecol Surv. 2008;63(1):39–48.
74. Weghofer A et al. Lack of association between polycystic ovary syndrome and embryonic aneuploidy. Fertil Steril. 2007;88(4):900–5.
75. Alchami A, O'Donovan O, Davies M. PCOS: diagnosis and management of related infertility. Obstet Gynaecol Reprod Med. 2015;25(10):279–82.
76. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010;203(3):201 e1–5.
77. Carreau AM, Baillargeon JP. PCOS in adolescence and type 2 diabetes. Curr Diab Rep. 2015;15(1):564.
78. Roe AH et al. Using the androgen excess-PCOS society criteria to diagnose polycystic ovary syndrome and the risk of metabolic syndrome in adolescents. J Pediatr. 2013;162(5):937–41.
79. Teede HJ et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Aust. 2011;195(6):S65–112.
80. Walls ML et al. In vitro maturation as an alternative to standard in vitro fertilization for patients diagnosed with polycystic ovaries: a comparative analysis of fresh, frozen and cumulative cycle outcomes. Hum Reprod. 2015;30(1):88–96.
81. Junk SM, Yeap D. Improved implantation and ongoing pregnancy rates after single-embryo transfer with an optimized protocol for in vitro oocyte maturation in women with polycystic ovaries and polycystic ovary syndrome. Fertil Steril. 2012;98(4):888–92.
82. Lindenberg S. New approach in patients with polycystic ovaries, lessons for everyone. Fertil Steril. 2013;99(5):1170–2.
83. Ganor-Paz Y et al. What is the best treatment for women with polycystic ovarian syndrome and high LH/FSH ratio? A comparison among in vitro fertilization with GnRH agonist, GnRH antagonist and in vitro maturation. J Endocrinol Invest. 2016;39(7):799–803.
84. Costello MF, Ledger WL. Evidence-based management of infertility in women with polycystic ovary syndrome using surgery or assisted reproductive technology. Future Med. 2012;8(3):291–300.

85. Reindollar RH et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010;94(3):888–99.
86. Franks S. When should an insulin sensitizing agent be used in the treatment of polycystic ovary syndrome? Clin Endocrinol (Oxf). 2011;74(2):148–51.
87. Wild RA et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab. 2010;95(5):2038–49.
88. Legro RS et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(12):4565–92.
89. Bergh CM, Moore M, Gundell C. Evidence-based management of infertility in women with polycystic ovary syndrome. J Obstet Gynecol Neonatal Nurs. 2016;45(1):111–22.
90. Tang T et al. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2012;5:CD003053.
91. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subertility (Review). The Cochrane Library. 2010:1–135.
92. Romualdi D et al. Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Fertil Steril. 2010;93(7):2303–10.
93. Tang T, Balen AH. Use of metformin for women with polycystic ovary syndrome. Hum Reprod Update. 2013;19(1):1.
94. Chambers GM et al. Is in vitro fertilisation more effective than stimulated intrauterine insemination as a first-line therapy for subfertility? A cohort analysis. Aust N Z J Obstet Gynaecol. 2010;50(3):280–8.
95. Walls M et al. IVF versus ICSI for the fertilization of in-vitro matured human oocytes. Reprod Biomed Online. 2012;25(6):603–7.
96. El Hachem H et al. Live birth after frozen-thawed oocytes matured in vitro in a PCOS patient: a model for improving implantation rates in IVM cycles and objectively assessing the real potential of development of frozen oocytes matured in vitro. Gynecol Endocrinol. 2014;30(6):415–8.

Chapter 15
Digestive Autoimmune Diseases: Inflammatory Bowel Disease

Incidence

Inflammatory bowel diseases (IBDs) predominantly affect younger patients of reproductive age [1]. Studies estimate that approximately 1.2 million people in the United States and 3.7 million people in Europe suffer from IBD, and in most parts of the world, IBD incidence rates increase over time [2–4]. Ulcerous colitis (UC) occurs slightly more frequently in men (60%), whereas CD occurs 20–30% more frequently in women, particularly in high-incidence areas [5]. Crohn's disease (CD) commonly first presents in teenagers and young adults.

Definition

IBDs are a group of chronic inflammatory conditions mainly of the colon and small intestine. CD and ulcerative colitis (UC) are the most frequent types of IBD [6, 7] both of which are complex diseases which arise as a result of the interaction of environmental, genetic, and immunological factors.

On the basis of a genetic susceptibility host, an excessive mucosal immune response toward the enteric microbiota plays a role for the initiation and perpetuation of intestinal inflammation [2, 6, 8–14]. It is increasingly thought that alterations of immunological reactions of the patients to their own enterable bacteria (microfilm) contribute to inflammation. Both pathologies are characterized by mucosal and submucosal inflammation, perpetuated by infiltration of activated leukocytes [13].

Common features of the two conditions include primary localization to the GI tract, a chronic course with alternating periods of remission and recurrence, inflammatory infiltration of the bowel wall, association with systemic and extraintestinal manifestations, and unknown etiology [15]. However, UC and CD also exhibit several individual features that distinguish them as separate diseases.

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_15

Crohn's Disease

CD is an autoimmune disorder characterized by transmural and discontinuous inflammation that may affect any part of the GI tract from the mouth to the anus, typically with rectal sparing. In addition, fistulous tracts are often formed in CD that allow for abnormal communication between the bowel and internal organs or the skin [13, 16]. The most commonly affected area is the terminal ileum and cecum (55%). Other areas include small bowel disease (11–48%), colon disease (19–51%), and combined small and large intestine (26–48%) [7, 17, 18]. The active disease is categorized into mild, moderate, and severe localized ileocecal disease, colonic disease, extensive small bowel disease, and esophageal and gastroduodenal disease [13]. CD cannot cure by any operation. A lifelong intake of drugs is mostly necessary and essential [13].

Ulcerative Colitis

It is characterized for confinement of disease activity to the large intestine with universal rectal involvement and continuous mucosal inflammation [13]. UC is graded into four disease activities (mild, moderate, severe, and remission) and divided into three different distribution patterns (proctitis, left sided, pancolitis). The severity of the disease is classified by a clinical activity index (CAI)—Rachmilewitz index or Mayo score, including stool frequency, rectal bleeding, endoscopic activity of the colon, and physician rating of disease activity [13]. The therapeutic goal in UC is to induce steroid-free clinical long-term remission or to increase intervals of acute flare [19]. Cancer surveillance in UC patients is strongly recommended as these individuals have an elevated risk to develop a colon cancer within 10 years. Advanced endoscopic and imaging techniques are warranted to optimize the diagnosis as cancer in UC is a clear indication for surgery [13, 19, 20]. UC has the possibility to be cured by a total colectomy.

The similarities between the two conditions point to a common immunogenetic background [15].

Diagnosis

Current diagnosis of IBD relies on the clinical, endoscopic, radiological, histological, and biochemical features; in the majority of cases, endoscopic findings and histological examination of tissue biopsies provides a specific diagnosis of UC or CD [21, 22].

Etiology and Pathophysiology

CD and UC are considered to be multifactorial diseases, and the underlying pathological process seems to be a combination of genetic predisposition and immunologic disturbances [4]. Studies of experimental animal models of IBD show that the presence of gut bacteria is essential in inflammation initiation, and there is no disease onset in germfree mice [4, 23]. Pathogenesis of the IBD is characterized by various genetic abnormalities that lead to overly aggressive altered immune response, triggered by heterogeneous environmental factors under the influence of the commensal intestinal microbiota. Only in correlation of those four mentioned main factors a disbalance of the gastrointestinal tract develops, leading to chronic inflammation with all its consequences and complications [4]. The role of the intestinal microbiota in the pathogenesis of IBD still remains unclear, but even though some enteric bacteria are detrimental and some are protective, their involvement in the pathogenesis of IBD is unquestionable [4]. We may say that the precise etiology of IBD is still unknown, but several factors that make a major contribution to disease pathogenesis have been identified [10].

Genetics

There is strong evidence to suggest a genetic basis for IBD, including familial clustering and racial and ethnic differences in risk for IBD. Ten to twenty percent of affected individuals will have family history of IBD, with the highest risk among first-degree relatives [13]. 163 IBD susceptibility loci were confirmed which means that 163 different alleles may increase the susceptibility to the disease. These 163 loci explain from 8.2% to a 13.6% of variance in CD and 4.1–7.5% in UC. These loci were related to 300 known genes. The most well-known and frequent gene associated with CD is the NOD2/CARD15 gene [13, 24–26].

Environmental Factors

There is evidence that IBD is primarily a disease of the developed countries. The rise in certain regions (i.e., India, China) parallelizes the industrialization of these countries. It seems that environmental factors may influence the normal intestinal commensal flora and thus trigger an inappropriate mucosal immune response [13]. Smoking and infections in childhood may trigger IBD especially CD [13, 27–29]. Smoking has a negative effect on the course of CD [1] and also increases the risk of developing the pathology. Moreover, CD patients who start or continue smoking

after disease diagnosis are at risk for poorer outcomes such as higher therapeutic requirements and disease-related complications, as compared to those patients who quit smoking or who never smoked [21]. Studies have also reported an association between early life exposure to antibiotics (in the first year of subject's life) and CD development due to early childhood dysbiosis. Other risk factors are use of antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), stress, infection, and diet. Until now only smoking and appendectomy have been clearly linked with the risk of developing IBD [4, 30], and smoking remains the most important environmental factor in IBD.

Immune System

The intestinal immune system defends against pathogens and entry of excessive intestinal microbes; simultaneously, a state of immune tolerance to resident intestinal microbes must be maintained. Perturbation of this balance is associated with intestinal inflammation and is thought to predispose humans to IBD. The immune system continuously monitors resident microbiota and utilizes constitutive antimicrobial mechanisms to maintain immune homeostasis. There is an increasing evidence that intestinal microbes influence host immune development, immune responses, and susceptibility to human diseases such as IBD [8]. An imbalanced intestinal immune defense and intestinal immune tolerance are one of the risks for developing IBD [13].

Disease Presentation

Gastrointestinal Symptoms and Extraintestinal Symptoms

The most common symptoms of IBD are:

- Diarrhea
- Presence of blood in the stool (more frequently in UC)
- Abdominal pain
- Weight loss (more frequently in CD)
- Systemic symptoms [21]

CD becomes symptomatic when lesions are extensive or distal, associated with a systemic inflammatory reaction, or when they are complicated by strictures or abscesses and fistulas. The disease course is generally distinguished by a sequence of flare-up episodes and remissions of varying durations, whereas 10–15% of patients undergo a chronic, continuous disease course [31]. Colonic disease usually has many symptoms, whereas ileal disease can remain latent for

several years. Arthritis, erythema nodosum, iritis and uveitis, aphthous stomatitis, and pyoderma gangrenosum are some of the extraintestinal manifestations [32, 33]. There is no relationship between symptoms and progression of anatomic damage. Short, uncomplicated ileitis can cause refractory abdominal pain and fatigue. Mucosal healing is associated with sustained clinical remission, less need for steroid therapy, and reduced rates of hospitalization and surgical resection [5, 34].

Gastrointestinal Symptoms Related to Menstrual Cycle

It is estimated that approximately 75% of women at the reproductive age experience GI symptomatology during different phases of the menstrual cycle [35, 36]; this may be explained based on the fact that there are sex hormone receptors in the intestinal smooth muscle. Ovarian hormones alter pain perception and visceral hypersensitivity [37]. The variation in GI symptomatology during menstrual cycle in patients with IBD has been investigated [38]. Several studies [38, 39] have reported worsening of GI symptoms, mostly diarrhea, in IBD patients during the menstrual phase. Also, the majority of women with underlying IBD experience a cyclical change in their GI symptoms during different phases of the menstrual cycle. However, definite data are lacking on whether this is a true disease exacerbation or normal physiological variation [38]. As therapies used to treat menstrual disorders such as dysmenorrhea including nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills (OCP) may influence the disease course of IBD [38, 39]. In addition, the management of IBD patients who experience worsening of their symptoms corresponding to the menstrual cycle could complicate the diagnosis of acute flare [35]. The diagnosis of IBD is associated with a delay in menarche as well as menstrual function irregularities including alterations in cycle length and the duration of flow. Understanding the influence of menstrual function on IBD disease activity and vice versa and the maintenance of normal menstrual function in those patients is important in improving overall reproductive health and fertility and outcome of IBD [35].

Psychological Aspects

Inflammatory bowel disease is a chronic, heterogenic, and lifelong illness with a high potential of individual and social disability; psychosocial issues are a significant dimension of IBD, chronic conditions of the gastrointestinal tract with an unknown etiology and unpredictable course [40]. There is a growing body of evidence demonstrating the role of stress, anxiety, and depression in IBD presentation and progression [40–42].

Cervical Dysplasia

Bhatia et al. published on 2006 that diagnosis of IBD in women is related to an increased risk of abnormal Pap smear. Patients with IBD, a group of autoimmune diseases with or without immunosuppression, carry a higher risk for developing cervical abnormalities, as more than 18% of patients in IBD group had abnormal Pap smears compared to 5% in the matched control group [43].

Complications

Both Crohn's disease (CD) and ulcerative colitis (UC) are associated with various kinds of complications. A direct causal relationship exists between disease duration and development of complications. However, CD is frequently related with the formation of fistulae and abscess due to its transmural nature, while UC is often accompanied by the results of severe inflammations such as toxic megacolon [44].

Fistula

It is a major complication of CD which is associated with high morbidity and mortality due to sepsis, malnutrition, and fluid and electrolyte imbalance. Around one-third of CD patients have fistulizing disease after 10 years from diagnosis. Fistula is defined as pathologic connection between the gastrointestinal tract and adjacent organs. Fistula can involve the small or large bowels, skin, bladder, vagina, and any other parts nearby in the severe inflammation of disease. The majority of fistula in CD is external or perianal lesion [44].

Abscess

Abscess formation is one of the most serious complications in patients with inflammatory bowel disease. About 7–28% of CD patients experience this complication during lifetime [44].

Stricture

Inflammatory bowel disease is frequently complicated by the formation of strictures.

Toxic Megacolon

Any inflammatory conditions of the colon including CD can lead to this infrequent complication. It is defined as segmental or total colonic distension of more than 6 cm in diameter with signs of acute colitis and systemic toxicity. Ten percent of UC and 2.3% of CD patients with hospitalization showed toxic megacolon. It is postulated that severe inflammation and damage of the colonic wall are the main causes of complication development.

Disease Management

The IBD represents a model of multidisciplinary management. Timing is the key for proper management of IBD patients.

Laboratory Tests

Laboratory Findings

- Increase of unspecific inflammatory markers as C-reactive protein (CRP) (activity marker) and erythrocyte sedimentation rate (ESR)
- Iron deficiency and anemia in different severities
- Specific cytokines [13]

Serological Markers

There is no usefulness of serological markers in monitoring the treatment of IBD patients [22]. There are two main groups of serologic markers: antibodies targeting microbial antigens and autoantibodies; these antibodies have limited sensitivity.

Calprotectin Level in Feces

Produced from granulocytes is a useful marker to measure disease activity and can predict disease recurrence. It is more precise than the common used markers like CRP and ESR [13, 45].

Medical Treatment

The heterogeneous nature of IBD implicates heterogeneous therapeutic strategies. Current therapies include the use of corticosteroids, anti-inflammatories, immune-suppressive drugs, antibiotics, and biologics [13]. According to the severity of CD, therapy strategies include nutritional approaches, anti-inflammatory drugs, immunosuppression, chemotherapy, and biologics. The therapeutic decision is influenced by the extent of severity, presence of septic complications, and extraintestinal manifestations. Medical treatment of IBD has to be individualized to each patient. The decision of what kind of drugs and what route administered (oral, rectal, intravenous) depends on factors including the type, the localization, and severity of the patient's disease. IBD may require immunosuppression to control symptoms such as prednisolone, thiopurines, calcineurin, or sometimes folic acid inhibitors or biologics like TNF-α inhibitors or anti-integrin antibodies. For both types of disease (CD, UC), the same drugs are available, but they differ in their preference in efficacy between CD and UC as 5-aminosalicylic acid for UC or budesonide (topical steroids) for ileocecal CD [13]. In both diseases, medical treatment has the main role. Immunomodulators and biological medications, alone or in combination, form the core therapeutic strategy to induce and maintain remission in moderate-to-severe IBD [46, 47]. Regular gynecological screening for cervical cancer is strongly recommended for women with IBD, especially if treated with immunomodulators [IMs] [38, 43, 48–51]. Methotrexate is FDA category X47 and is contraindicated during conception and pregnancy. Because of the drug's long half-life, women should not attempt conception within 3–6 months of methotrexate use [52].

The topical use of 5-ASA (mesalazine) is still the treatment of choice for proctitis or left-sided mild-to-moderate disease or topical steroids although topical steroids were found to be less effective than topical mesalazine [53]. The systemic use of aminosalicylic derivatives is additionally recommended in more extensive or severe cases [13, 19]. Steroids have a thoroughly established efficacy profile for the induction of remission [54]. For severe UC, and in patients refractory to 5-ASA, the need for systemic steroids is a general knowledge [13, 19, 55] combination of oral steroids, and 5-ASA in escalating doses in case of treatment failure with 5-ASA alone is strongly recommended [13, 54].

Nutritional therapy as supplementation to medical treatment may be helpful in induction and maintenance of remission or controlling symptoms especially in children [13, 56].

Surgery

Despite the incredible advance in the medical therapy for CD, surgery remains an important component in its management. In some phases of the natural history of IBD, surgery becomes an important therapeutic tool. For acute and severe IBD, the

surgery can be a salvage procedure. Today, the laparoscopic approach plays an important role [7]. Gastrointestinal luminal endoscopy is of paramount importance for the management of IBD patients [2]. Surgery generally is reserved for failure of medical treatment (refractory disease) or complications [13, 17, 57] as stricture, abscess, fistula, hemorrhage, or malignant transformation [16]. For these reasons, about 80% of all CD patients will require surgical treatment during their lifetime, and about 15–20% of patients will undergo surgery within the first year after diagnosis [7, 16, 18, 58]. Surgical treatment of CD is solely symptomatic. In addition, medical therapy always precedes surgery and almost always continues afterward. Elective surgery is indicated in chronic therapy refractory cases or when signs of dysplasia are found. Here, the common surgery therapy is total proctocolectomy with ileal pouch–anal anastomosis (IPAA) [19, 59]. This surgical intervention may have a high curative potential in UC, but high rates (up to 20%) of postoperative complications are still emerging problems [19, 60, 61]. High-dose steroids should be weaned before surgery because they are a risk factor for complications [13, 59].

Up to now, there is no cure for IBD. Different treatments have limitations due to side effects, refractoriness, or unresponsiveness of the patients due to known and unknown causes. There are still a number of individuals in whom the current strategies are insufficient in controlling symptoms.

Effect on Fertility

IBDs significantly affect several reproductive aspects of human (female, male, couple) reproduction [1]. Moreover, further data are needed in order to develop guidelines for the clinical management of subjects of reproductive age with IBDs because very little is known on the overall effect of IBDs on human reproduction [1].

IBD incidence is highest between 20 and 35 years of age, with 50% of patients diagnosed before age 32, and 25% of women will have their first pregnancy after diagnosis [62], so we may conclude that affects predominantly female patients of childbearing age [48]. This coincides with the prime reproductive years; therefore, these patients are concerned about fertility and how it may be affected by their disease and related medical and surgical treatments [61, 63, 64].

Many questions regarding the impact of IBD and its treatment on fertility, fecundity, maternal and fetal health during pregnancy, delivery, breastfeeding safety, and childhood development are usually asked [52]. Lack of education and misconceptions regarding the effect of disease and/or treatment on reproductive outcome may lead to voluntary childlessness [48]. Reasons for the potentially reduced fertility in IBD are psychological problems and surgery-related problems [1]. “Voluntary childlessness” was the main cause of the reduced fertility rate (number of live births per woman) reported in IBD patients [1, 65]. The main reproductive concerns of IBD patients regarded pregnancy risks, drug-related teratogenicity or toxicity,

long-term risks, and IBD inheritance [1, 65]. Patients may choose not to have children due to several concerns, including the effect of pregnancy on disease, the possibility of passing on a diagnosis of IBD to a child, or the stress of raising a child in the setting of concomitant disease burden [66, 67]. Decrease in sexual function may also impact overall fertility, as IBD is related to poor body image, dyspareunia, and decreased sexual activity [68–71].

Women with inactive CD or UC non-operated appear to have normal fertility compared to general population [1, 77–79]. However, men and women with IBD are fearful of the disease's potential impact on fertility [65], and patient misperceptions contribute to the observed phenomenon of voluntary childlessness within the IBD population [72]. Although fertility in female patients with IBD does not appear to differ from the general population, they tend to have fewer children [65, 66].

In CD, fertility is normal or slightly reduced [1, 73, 74]; community-based and population-based studies suggest infertility rates of 5–14%, similar to that of the general population [74]. Active disease, however, may reduce fertility [73, 74]. Hypothesized mechanisms include poor nutrition, depression [75], decreased libido, and dyspareunia. In CD, this is only partially explained by voluntary childlessness as evidence suggests that these patients may have reduced fecundity either directly, such as via obstruction of fallopian tubes by adhesions or inflammation, or indirectly via surgical interventions [48, 76]. In some cases, fertility may normalize after induction of remission in women with CD [77]. Women with UC have normal fertility until they undergo surgery [1, 78]. The most significant factor influencing fertility in the IBD population is surgery, specifically total proctocolectomy with ileal pouch–anal anastomosis (IPAA); in women with UC, the ability to become pregnant is significantly reduced and increases female infertility threefold [61] due to adhesions in the pelvis and other surgical issues and secondary obstruction of the fallopian tubes or altering the normal tubo-ovarian relationship necessary for ovum capture and transport [1, 52, 79]. Women with IPAA mostly suffer a reduction in the probability of conception rather than complete infertility [1]. This subgroup of patients has an increased risk of infertility compared to the general IBD population, which is thought to be related to tubal factors secondary to surgery [61, 71, 80, 81] resulting in tubal infertility [82]. Supporting the hypothesis that tubal factors from surgery may play a role in infertility in women with IBD, it had been found that tubal factor infertility was more common in the CD population compared with the non-IBD population (24.5% vs 14.0%; P ¼ .05). Women with UC and CD achieve similar rates of live birth following IVF as the general infertility population [71, 83, 84]. IVF bypasses this factor and obviates the need for functional fallopian tubes. It is reassuring that adhesion-related factors potentially can be overcome by assisted reproductive techniques such as IVF [85].

The study of human reproduction includes not only the effects of IBDs and their treatment on pregnancy but also their effects on the menstrual cycle and hormonal patterns, on the subfertile women scheduled for ovulation induction cycles or assisted reproductive techniques (ARTs), on future reproductive potential in younger and/or adolescent women, and on male fertility, including data on semen parameters and libido/hormonal patterns [1].

Pregnancy Outcomes

Population-based studies demonstrate that women with IBD experience higher rates of preterm delivery, low birth weight, and small for gestational age infants, regardless of disease activity [52, 86–92]. Avoiding active disease will reduce the risk of adverse pregnancy outcomes [52]. The available medical evidence reassures that most of the IBD medications are safe or low risk during pregnancy and lactation and that the benefit of treatment outweighs the potential risks. Voluntary stopping IBD medications has shown to increase the risk for flares of IBD during pregnancy, which in turn increases the risk of adverse outcomes such as preterm birth, small for gestational age children, and fetal death [48, 93, 94]. Current recommendations are to induce remission before conception and continue appropriate medical therapies to maintain remission during pregnancy [95]. Data have shown that women who enter pregnancy with active disease are twice as likely to have active disease during pregnancy when compared with women with IBD who enter pregnancy in remission [85, 96]. The 2010 European Crohn's and Colitis Organization (ECCO) guidelines state "medical treatment for Crohn's disease (except methotrexate) should generally continue during pregnancy, because the benefits outweigh the risks of medication" [97]. Moreover, as complications and adverse pregnancy outcomes mainly occur in patients with active disease, the main concern should be to achieve remission before conception and maintain quiescent disease during pregnancy. Patients who received counseling regarding the benefits and risks of drug treatment before conception and during pregnancy were more likely to remain compliant [1, 98]. It is important to continue effective maintenance medications during pregnancy, as women who decrease or stop maintenance therapy have a greater risk of disease flare [99, 100]. Disease flares during pregnancy respond well to medical therapy, with response rates exceeding 80% even among severe flares requiring hospitalization [101]. Preconception optimization of the therapeutic regimen is critical to suppress disease activity and minimize the risk of relapse during pregnancy. Women should ideally be in sustained corticosteroid-free remission for at least 6 months in advance of conception. Immunomodulators and biologics may play a decisive role in the induction and maintenance of remission. With the exception of methotrexate, all effective immunomodulators and biologics may be continued before, during, and after pregnancy [52]. The US Food and Drug Administration (FDA) implemented new prescription drug and biological product labeling on June 30, 2015 [102]. The new labeling removes the pregnancy categories A, B, C, D, and X, replacing them with a summary of the risks of using a given drug during pregnancy and lactation [52, 102]. There may be a lack of knowledge, among both the provider and patient populations, on the importance of continuing medical therapies in women with IBD during conception and pregnancy to maintain remission [85]. The goals for successful reproductive outcomes in IBD population are correct counseling and disease remission [1].

Male Fertility

Active disease, IBD treatment, and psychological factors affect male reproductive and sexual function [103]. Most male IBD patients considered "maintaining remission" as important at conception [104].

Several mechanisms have been described explaining male infertility seen in patients with IBD. The most commonly studied etiology is impairment of spermatogenesis by therapeutic agents [105]. It is recognized that male infertility is often impacted with therapeutic drugs used to treat inflammatory bowel disease; however, the effect of the paternal drug exposure at the time of conception and exposure in uterus should also be considered to counsel patients appropriately [105]. Only one report [106] described the reproductive outcome following intracytoplasmic sperm injection (ICSI) for male factor infertility associated with CD and 6-mercaptopurine (6-MP) chemotherapy. The authors [106] reported the first successful birth after ICSI for severe oligozoospermia associated with CD [1].

IVF Results

Age and BMI are associated with successful IVF. Though the length of disease and possibly disease activity in patients with UC may also be associated with live birth, further study is needed to confirm these results. Patients with IBD should be in remission before attempting IVF, similar to recommendations that patients be in remission prior to getting pregnant. Prior surgical treatment and current medications in both UC and CD did not appear to be associated with the success of IVF. Clinically, this information is relevant to practitioners and patients when discussing medical and surgical treatment of IBD and the potential success of IVF [71].

Fertility Preservation

In the few last years, only two studies [107, 108] investigated the ovarian reserve status in CD women, as reflected by serum AMH. The first study [107] showed that women with CD do not have severe ovarian reserve alterations compared with a control population. However, age $\geq$30 years and a colonic location of the disease could be associated with an accelerated loss of follicles. Another study [108] confirmed that serum AMH levels of reproductive-age women with CD were significantly lower compared with the controls, and the Crohn's disease activity index (CDAI) and AMH were inversely correlated. Thus, these data could encourage gastroenterologists to inform CD women of the risk of delaying childbirth.

At the moment, there are no established guidelines for the preservation of fertility in women with IBD undergoing surgery. Further data is needed regarding the management of these patients [1].

However, an effective strategy should be based on the following principles:

1. Selection of patients with a specific clinical indication for surgery
2. Evaluation of the patient based on factors predictive of ovarian reserve [i.e., age, anti-Müllerian hormone (AMH), antral follicle count]
3. Surgery that is as minimally destructive of the radical pelvic anatomy as possible [1]

Some of the apparent adverse effects of pouch surgery among women with UC may therefore be due to family planning as women who have pouch surgery have a higher fertility rate before surgery, suggesting women electively complete their families before pouch surgery [63]. Women should be advised about their potential fertility according to their existing reproductive history, presence of acute flares, and need for surgical intervention with pouch and nonpouch surgery [63].

Better patient education through multidisciplinary classes encompassing gastroenterologists, obstetricians and gynecologists, midwives, IBD specialist nurses, and the IBD association may lead to the much desired improved knowledge, with the much desired improving effect on women's health [48].

References

1. Palomba S, Sereni G, Falbo A, Beltrami M, Lombardini S, Boni MC, et al. Inflammatory bowel diseases and human reproduction: a comprehensive evidence-based review. World J Gastroenterol. 2014;20(23):7123–36.
2. Tontini GE, Rath T, Neumann H. Advanced gastrointestinal endoscopic imaging for inflammatory bowel diseases. World J Gastroenterol. 2016;22(3):1246–59.
3. Kappelman MD, Moore KR, Allen JK, Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. Dig Dis Sci. 2013;58(2):519–25.
4. Lovasz BD, Golovics PA, Vegh Z, Lakatos PL. New trends in inflammatory bowel disease epidemiology and disease course in Eastern Europe. Dis Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2013;45(4):269–76.
5. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785–94.
6. Leitner GC, Vogelsang H. Pharmacological- and non-pharmacological therapeutic approaches in inflammatory bowel disease in adults. World J Gastrointestinal Pharmacol Therapeutics. 2016;7(1):5–20.
7. Solina G, Mandala S, La Barbera C, Mandala V. Current management of intestinal bowel disease: the role of surgery. Updat Surg. 2016;68(1):13–23.
8. Abraham C, Medzhitov R. Interactions between the host innate immune system and microbes in inflammatory bowel disease. Gastroenterology. 2011;140(6):1729–37.
9. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annu Rev Immunol. 2010;28:573–621.
10. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. Nature. 2011;474(7351):298–306.

11. Neurath MF. Cytokines in inflammatory bowel disease. Nat Rev Immunol. 2014;14(5):329–42.
12. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011;474(7351):307–17.
13. Leitner GC, Vogelsang H. Pharmacological- and non-pharmacological therapeutic approaches in inflammatory bowel disease in adults. World J Gastr Pharmacol Th. 2016;7(1):5–20.
14. Mukhopadhya I, Hansen R, El-Omar EM, Hold GL. IBD-what role do Proteobacteria play? Nat Rev Gastroenterol Hepatol. 2012;9(4):219–30.
15. Bamias G, Pizarro T, Cominelli F. New paradigms in the pathogenesis of IBD. Inflamm Bowel Dis. 2011;18:41–57.
16. Maggiori L, Panis Y. Laparoscopy in Crohn's disease. Best Pract Res Clin Gastroenterol. 2014;28(1):183–94.
17. Aarons CB. Laparoscopic surgery for crohn disease: a brief review of the literature. Clin Colon Rectal Surg. 2013;26(2):122–7.
18. Lim JY, Kim J, Nguyen SQ. Laparoscopic surgery in the management of Crohn's disease. World J Gastrointestinal Pathophysiol. 2014;5(3):200–4.
19. Meier J, Sturm A. Current treatment of ulcerative colitis. World J Gastroenterol. 2011;17(27):3204–12.
20. Matsumoto T, Kudo T, Jo Y, Esaki M, Yao T, Iida M. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. Gastrointest Endosc. 2007;66(5):957–65.
21. Gheorghe C, Pascu O, Gheorghe L, Iacob R, Dumitru E, Tantau M, et al. Epidemiology of inflammatory bowel disease in adults who refer to gastroenterology care in Romania: a multicentre study. Eur J Gastroenterol Hepatol. 2004;16(11):1153–9
22. Tesija KA. Serological markers of inflammatory bowel disease. Biomark Med. 2013;23:28–42.
23. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54 e42; quiz e30.
24. Gaya DR, Russell RK, Nimmo ER, Satsangi J. New genes in inflammatory bowel disease: lessons for complex diseases? Lancet. 2006;367(9518):1271–84.
25. Jess T, Riis L, Jespersgaard C, Hougs L, Andersen PS, Orholm MK, et al. Disease concordance, zygosity, and NOD2/CARD15 status: follow-up of a population-based cohort of Danish twins with inflammatory bowel disease. Am J Gastroenterol. 2005;100(11):2486–92.
26. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491(7422):119–24.
27. Mikhailov T-A. Breastfeeding and genetic factors in the etiology of inflammatory bowel disease in children. World J Gastroenterol. 2009;15(3):270.
28. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. Gastroenterol Hepatol. 2010;6(5):339–46.
29. Ng SC, Woodrow S, Patel N, Subhani J, Harbord M. Role of genetic and environmental factors in British twins with inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(4):725–36.
30. Lakatos L, Kiss LS, David G, Pandur T, Erdelyi Z, Mester G, et al. Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002-2006. Inflamm Bowel Dis. 2011;17(12):2558–65.
31. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol. 1995;30(7):699–706.
32. Peyrin-Biroulet L, Loftus Jr EV, Colombel JF, Sandborn WJ. Long-term complications, extraintestinal manifestations, and mortality in adult Crohn's disease in population-based cohorts. Inflamm Bowel Dis. 2011;17(1):471–8.
33. Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106(1):110–9.

34. Froslie KF, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412–22.
35. Bharadwaj S, Kulkarni G, Shen B. Menstrual cycle, sex hormones in female inflammatory bowel disease patients with and without surgery. J Dig Dis. 2015;16(5):245–55.
36. Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the menstrual cycle? Br J Obstet Gynaecol. 1998;105(12):1322–5.
37. Bjornsson B, Orvar KB, Theodors A, Kjeld M. The relationship of gastrointestinal symptoms and menstrual cycle phase in young healthy women. Laeknabladid. 2006;92(10):677–82.
38. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. Am J Gastroenterol. 2008;103(3):631–6.
39. Lim SM, Nam CM, Kim YN, Lee SA, Kim EH, Hong SP, et al. The effect of the menstrual cycle on inflammatory bowel disease: a prospective study. Gut and liver. 2013;7(1):51–7.
40. Loftus CG, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton 3rd LJ, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis. 2007;13(3):254–61.
41. Stewenius J, Adnerhill I, Ekelund G, Floren CH, Fork FT, Janzon L, et al. Ulcerative colitis and indeterminate colitis in the city of Malmo, Sweden. A 25-year incidence study. Scand J Gastroenterol. 1995;30(1):38–43.
42. Manousos ON, Giannadaki E, Mouzas IA, Tzardi M, Koutroubakis I, Skordilis P, et al. Ulcerative colitis is as common in Crete as in northern Europe: a 5-year prospective study. Eur J Gastroenterol Hepatol. 1996;8(9):893–8.
43. Bhatia J, Bratcher J, Korelitz B, Vakher K, Mannor S, Shevchuk M, et al. Abnormalities of uterine cervix in women with inflammatory bowel disease. World J Gastroenterol. 2006;12(38):6167–71.
44. Chan Heyson C-h, Kim DH, Lung PFC, Cheon JH, Ng SC. Complications of inflammatory bowel disease. In: Atlas of Inflammatory Bowel Diseases. W.H. Kim, J.H. Cheon (eds.). Berlin, Heidelberg: Springer, 2015. p. 175–86.
45. Xiang J-Y. Clinical value of fecal calprotectin in determining disease activity of ulcerative colitis. World J Gastroenterol. 2008;14(1):53.
46. Burger D, Travis S. Conventional medical management of inflammatory bowel disease. Gastroenterology. 2011;140(6):1827–37 e2.
47. Terdiman JP, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013;145(6):1459–63.
48. Ellul P, Zammita SC, Katsanos KH, Cesarini M, Allocca M, Danese S, et al. Perception of reproductive health in women with inflammatory bowel disease. J Crohn's Colitis. 2016;10(8):886–91.
49. Rungoe C, Simonsen J, Riis L, Frisch M, Langholz E, Jess T. Inflammatory bowel disease and cervical neoplasia: a population-based nationwide cohort study. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterolo Asso. 2015;13(4):693–700 e1.
50. Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's Colitis. 2014;8(6):443–68.
51. Sanchez-Tembleque MD, Corella C, Perez-Calle JL. Vaccines and recommendations for their use in inflammatory bowel disease. World J Gastroenterol. 2013;19(9):1354–8.
52. McConnell RA, Mahadevan U. Use of immunomodulators and biologics before, during, and after pregnancy. Inflamm Bowel Dis. 2016;22(1):213–23.
53. Cottone M, Renna S, Modesto I, Orlando A. Is 5-ASA still the treatment of choice for ulcerative colitis? Curr Drug Targets. 2011;12(10):1396–405.
54. Probert C. Steroids and 5-aminosalicylic acids in moderate ulcerative colitis: addressing the dilemma. Therapeutic Adv Gastroenterol. 2013;6(1):33–8.
55. Regueiro M, Loftus Jr EV, Steinhart AH, Cohen RD. Clinical guidelines for the medical management of left-sided ulcerative colitis and ulcerative proctitis: summary statement. Inflamm Bowel Dis. 2006;12(10):972–8.

56. Donnellan CF, Yann LH, Lal S. Nutritional management of Crohn's disease. Ther Adv Gastroenterol. 2013;6(3):231–42.
57. Malafosse M. Crohn's disease: current surgical treatment. Bulletin de l'Academie nationale de medecine. 2007;191(6):1143–56; discussion 57–8.
58. Tavernier M, Lebreton G, Alves A. Laparoscopic surgery for complex Crohn's disease. J Vis Surg. 2013;150(6):389–93.
59. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management (Spanish version). Rev Gastroenterol Mex. 2015;80(1):32–73.
60. Hueting WE, Buskens E, van der Tweel I, Gooszen HG, van Laarhoven CJ. Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients. Dig Surg. 2005;22(1-2):69–79.
61. Waljee A, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. Gut. 2006;55(11):1575–80.
62. Beaulieu DB, Kane S. Inflammatory bowel disease in pregnancy. World J Gastroenterol. 2011;17(22):2696–701.
63. Ban L, Tata LJ, Humes DJ, Fiaschi L, Card T. Decreased fertility rates in 9639 women diagnosed with inflammatory bowel disease: a United Kingdom population-based cohort study. Aliment Pharmacol Ther. 2015;42(7):855–66.
64. Rajaratnam SG, Eglinton TW, Hider P, Fearnhead NS. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. Int J Color Dis. 2011;26(11):1365–74.
65. Mountifield R, Bampton P, Prosser R, Muller K, Andrews JM. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. Inflamm Bowel Dis. 2009;15(5):720–5.
66. Marri SR, Ahn C, Buchman AL. Voluntary childlessness is increased in women with inflammatory bowel disease. Inflamm Bowel Dis. 2007;13(5):591–9.
67. Manosa M, Navarro-Llavat M, Marin L, Zabana Y, Cabre E, Domenech E. Fecundity, pregnancy outcomes, and breastfeeding in patients with inflammatory bowel disease: a large cohort survey. Scand J Gastroenterol. 2013;48(4):427–32.
68. Muller KR, Prosser R, Bampton P, Mountifield R, Andrews JM. Female gender and surgery impair relationships, body image, and sexuality in inflammatory bowel disease: patient perceptions. Inflamm Bowel Dis. 2010;16(4):657–63.
69. Marin L, Manosa M, Garcia-Planella E, Gordillo J, Zabana Y, Cabre E, et al. Sexual function and patients' perceptions in inflammatory bowel disease: a case-control survey. J Gastroenterol. 2013;48(6):713–20.
70. Wikland M, Jansson I, Asztely M, Palselius I, Svaninger G, Magnusson O, et al. Gynaecological problems related to anatomical changes after conventional proctocolectomy and ileostomy. Int J Color Dis. 1990;5(1):49–52.
71. Oza SS, Pabby V, Dodge LE, Hacker MR, Fox JH, Moragianni VA, et al. Factors associated with the success of in vitro fertilization in women with inflammatory bowel bisease. digestive diseases and sciences. 2016;61(8):2381–8.
72. Tavernier N, Fumery M, Peyrin-Biroulet L, Colombel JF, Gower-Rousseau C. Systematic review: fertility in non-surgically treated inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(8):847–53.
73. Khosla R, Willoughby CP, Jewell DP. Crohn's disease and pregnancy. Gut Liver. 1984;25(1):52–6.
74. Hudson M, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. Int J Gynaecol Obstetrics Off Organ Inter Federation Gynaecol Obstetrics. 1997;58(2):229–37.
75. Timmer A, Bauer A, Dignass A, Rogler G. Sexual function in persons with inflammatory bowel disease: a survey with matched controls. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Asso. 2007;5(1):87–94.

76. Nielsen MJ, Norgaard M, Holland-Fisher P, Christensen LA. Self-reported antenatal adherence to medical treatment among pregnant women with Crohn's disease. Aliment Pharmacol Ther. 2010;32(1):49–58.
77. Baiocco PJ, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. J Clin Gastroenterol. 1984;6(3):211–6.
78. Dubinsky M, Abraham B, Mahadevan U. Management of the pregnant IBD patient. Inflamm Bowel Dis. 2008;14(12):1736–50.
79. Diamond MP, Freeman ML. Clinical implications of postsurgical adhesions. Hum Reprod Update. 2001;7(6):567–76.
80. Oresland T, Palmblad S, Ellstrom M, Berndtsson I, Crona N, Hulten L. Gynaecological and sexual function related to anatomical changes in the female pelvis after restorative proctocolectomy. Int J Color Dis. 1994;9(2):77–81.
81. Cornish JA, Tan E, Teare J, Teoh TG, Rai R, Darzi AW, et al. The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. Dis Colon Rectum. 2007;50(8):1128–38.
82. Arkuran C, McComb P. Crohn's disease and tubal infertility: the effect of adhesion formation. Clin Exp Obstet Gynecol. 2000;27(1):12–3.
83. Oza SS, Pabby V, Dodge LE, Moragianni VA, Hacker MR, Fox JH, et al. In vitro fertilization in women with inflammatory bowel disease is as successful as in women from the general infertility population. Clini Gastroenterol Hepatol Off Clini Pract J Am Gastroenterol Asso. 2015;13(9):1641–6 e3.
84. Pabby V, Oza SS, Dodge LE, Hacker MR, Moragianni VA, Correia K, et al. In vitro fertilization is successful in women with ulcerative colitis and ileal pouch anal anastomosis. Am J Gastroenterol. 2015;110(6):792–7.
85. Long MD. Infertility in inflammatory bowel diseases: a cause for hope? Clin Gastroenterol Hepatol Off Clini Pract J Am Gastroenterol Asso. 2015;13(9):1647–9.
86. Norgard B, Fonager K, Sorensen HT, Olsen J. Birth outcomes of women with ulcerative colitis: a nationwide Danish cohort study. Am J Gastroenterol. 2000;95(11):3165–70.
87. Dominitz JA, Young JC, Boyko EJ. Outcomes of infants born to mothers with inflammatory bowel disease: a population-based cohort study. Am J Gastroenterol. 2002;97(3):641–8.
88. Stephansson O, Larsson H, Pedersen L, Kieler H, Granath F, Ludvigsson JF, et al. Crohn's disease is a risk factor for preterm birth. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Asso. 2010;8(6):509–15.
89. Molnar T, Farkas K, Nagy F, Lakatos PL, Miheller P, Nyari T, et al. Pregnancy outcome in patients with inflammatory bowel disease according to the activity of the disease and the medical treatment: a case-control study. Scand J Gastroenterol. 2010;45(11):1302–6.
90. Stephansson O, Larsson H, Pedersen L, Kieler H, Granath F, Ludvigsson JF, et al. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. Inflamm Bowel Dis. 2011;17(3):795–801.
91. Getahun D, Fassett MJ, Longstreth GF, Koebnick C, Langer-Gould AM, Strickland D, et al. Association between maternal inflammatory bowel disease and adverse perinatal outcomes. J Perinatol Off J Calif Perinat Assoc. 2014;34(6):435–40.
92. Broms G, Granath F, Linder M, Stephansson O, Elmberg M, Kieler H. Birth outcomes in women with inflammatory bowel disease: effects of disease activity and drug exposure. Inflamm Bowel Dis. 2014;20(6):1091–8.
93. Bush MC, Patel S, Lapinski RH, Stone JL. Perinatal outcomes in inflammatory bowel disease. J Maternal-Fetal Neonat Med Off J Eur Asso Perinatal Med F Asia Oceania Perinatal Soc Inter Soc Perinatal Obstet. 2004;15(4):237–41.
94. Elbaz G, Fich A, Levy A, Holcberg G, Sheiner E. Inflammatory bowel disease and preterm delivery. Inter J Gynaecol Obst Off Organ Inter Fed Gynaecol Obstetrics. 2005;90(3):193–7.
95. Mahadevan U, Kane S. American gastroenterological association institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology. 2006;131(1):278–82.

96. Abhyankar A, Ham M, Moss AC. Meta-analysis: the impact of disease activity at conception on disease activity during pregnancy in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(5):460–6.
97. Nguyen GC, Boudreau H, Harris ML, Maxwell CV. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Asso. 2009;7(3):329–34.
98. Julsgaard M, Norgaard M, Hvas CL, Buck D, Christensen LA. Self-reported adherence to medical treatment prior to and during pregnancy among women with ulcerative colitis. Inflamm Bowel Dis. 2011;17(7):1573–80.
99. Ujihara M, Ando T, Ishiguro K, Maeda O, Watanabe O, Hirayama Y, et al. Importance of appropriate pharmaceutical management in pregnant women with ulcerative colitis. BMC Res Notes. 2013;6:210
100. Julsgaard M, Norgaard M, Hvas CL, Grosen A, Hasseriis S, Christensen LA. Self-reported adherence to medical treatment, breastfeeding behaviour, and disease activity during the postpartum period in women with Crohn's disease. Scand J Gastroenterol. 2014;49(8):958–66.
101. Reddy D, Murphy SJ, Kane SV, Present DH, Kornbluth AA. Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. Am J Gastroenterol. 2008;103(5):1203–9.
102. Food and Drug Administration, HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. Fed Regist. 2014;79(233):72063–103.
103. Feagins LA, Kane SV. Sexual and reproductive issues for men with inflammatory bowel disease. Am J Gastroenterol. 2009;104(3):768–73.
104. Sato A, Naganuma M, Asakura K, Nishiwaki Y, Yajima T, Hisamatsu T, et al. Conception outcomes and opinions about pregnancy for men with inflammatory bowel disease. J Crohn's Colitis. 2010;4(2):183–8.
105. Sands K, Jansen R, Zaslau S, Greenwald D. Review article: the safety of therapeutic drugs in male inflammatory bowel disease patients wishing to conceive. Aliment Pharmacol Ther. 2015;41(9):821–34.
106. Sills ES, Tucker MJ. First experience with intracytoplasmic sperm injection for extreme oligozoospermia associated with Crohn's disease and 6-mercaptopurine chemotherapy. Asian J Androl. 2003;5(1):76–8.
107. Freour T, Miossec C, Bach-Ngohou K, Dejoie T, Flamant M, Maillard O, et al. Ovarian reserve in young women of reproductive age with Crohn's disease. Inflamm Bowel Dis. 2012;18(8):1515–22.
108. Senates E, Colak Y, Erdem ED, Yesil A, Coskunpinar E, Sahin O, et al. Serum anti-Mullerian hormone levels are lower in reproductive-age women with Crohn's disease compared to healthy control women. J Crohn's Colitis. 2013;7(2):e29–34.

Chapter 16
Breast Cancer

Incidence

Breast cancer is the most common non-cutaneous malignancy among women in the United States and worldwide. The estimated incidence of invasive breast cancer in the United States will be almost 232,000 and incidence of ductal carcinoma in situ exceeded 50,000 in 2015. Most of these women will be treated successfully, with an overall 5-year relative survival rate of 88.1% for breast cancer among women of all ages [1–4]. In the United States, breast cancer is the second leading cause of cancer-related death in women. Each year, a small number of men are diagnosed with and die from breast cancer. The overall rate of diagnosis of breast cancer began decreasing in 2000 and has remained steady in recent years, and the overall breast cancer death rate has dropped steadily over the past 20 years [5]. The incidence of breast cancer is highest in white women for most age groups, but African American women have higher incidence rates before 40 years of age and higher breast cancer mortality rates than women of any other racial/ethnic group in the United States at every age [5]. Globally, the highest BC incidence appears in high-income regions. However, lower incidence in Asiatic regions is changing dramatically into permanently increasing BC rates for both younger and older women [6].

The median age at diagnosis is 61 years, and 43% are older than 65 years at diagnosis; thus, cancer survivorship must be managed in coordination with comorbidities. Approximately 61% will have localized disease, for which survival outcomes are highest (5-year relative survival rates of 99% for localized-stage breast cancer *versus* 25% for distant-stage breast cancer) [2, 7]. Long-term survival is common after breast cancer treatment, with a 5-year survival rate of almost 90% [2, 7].

Breast cancer is a major public health problem which negatively impacts the quality of life of patients and their families, healthcare systems, and the whole society.

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_16

Every year, approximately 12,500 women under the age of 40 years are diagnosed with breast cancer in the United States [8], accounting for 7% of all women diagnosed with breast cancer [9]. Breast cancer represents four in ten female cancer survivors in the United States [8]. There is a 5-year relative survival rate of 87.1% among women younger than 45 years with a diagnosis of breast cancer [10]. Thus, most women with a diagnosis of breast cancer will become long-term survivors, making survivorship and quality-of-life issues important [1].

Natural History

The most common site of origin of breast cancer is the upper-outer quadrant, and metastasis to the ipsilateral axilla is the most common route of spread [11].

Risk Factors

Women's risk factors for breast cancer:

- *Increasing age*: age is the most significant risk factor for breast cancer [12].
- *Personal history of breast cancer and certain benign breast diseases* (proliferative changes, atypical hyperplasia): proliferative benign breast disease increases a risk for BC development, and dietary factors are known to influence the risks of benign breast disorder, particularly early in life [13].
- *Endogenous endocrine factors*: early menarche, late menopause, long menses duration, nulliparity, and late maternal age at first pregnancy (first pregnancy after age 30). The time period between menarche and first full-term pregnancy is the most susceptible for breast carcinogenesis [12], and lifestyle plays a crucial role in either preventing or, in contrast, facilitating the formation of premalignant lesions in functional breast tissue, depending on a balance between protective and destructive factors such as alcohol intake [14], inappropriate dietary habits, and low quality of meal and sleep deficits. Late first full-term pregnancy is a dominant risk factor for breast malignancies. Altered dietary habits and socioeconomical and environmental conditions that are usual altogether lead to synergistic effects resulting in early menarche (below 10 years), late menopause (over 50 years), and low number of children born. This dramatically increases the exposure to the hormonal stress, which breast tissues are particularly sensitive to extensively accumulating precancerous lesions over the extremely prolonged time of the hormonal stress exposure. This knowledge led to the consideration of a protective therapeutic approach by estrogen receptor blockers such as tamoxifen, raloxifene, and fulvestrant [15].
- *Exogenous hormones*: long-term use of combined hormone therapy. Oral contraceptives or birth control pills may increase BC risk, if used over the long

periods of time and actually for more than 5 years. Estrogen replacement therapy; the role of exogenous estrogens in the promotion of breast cancer is still controversial. The annual increased risk for an individual woman is still relatively small. The increased risk for breast cancer is apparent after 4 years of HRT use. HRT is highly effective in treating vasomotor symptoms with limited effective alternative therapies. In this setting, short-term use (<5 years) can be considered because data on short-term use does not show an increased association with breast cancer [15].

- *Prior exposure to radiation therapy* (history of radiation therapy to the chest): exposure to ionizing radiation such as occurs in treatment with radiation for Hodgkin disease poses a risk for breast cancer. The risk of breast cancer associated with radiation exposure decreases with increasing age at exposure [11].
- *Alcohol use*: alcohol consumption has been reported to increase breast cancer risk in a dose-related manner. Alcohol intake is most critical in the time period between menarche and first full-term pregnancy, which is the most susceptible one for breast carcinogenesis.
- *Obesity after menopause and abnormal BMI*: abnormal body weight may contribute to BC development and belongs to modifiable risk factors in the context of dietary intake and physical activity. In the term abnormal body weight, in which both too low and too high BMI are incorporated, therefrom, overweight and obese subjects are considered and investigated more frequently as being at high risk for BC; the association between the weight and breast cancer risk is highly individual and contextual (genetic predisposition, age, hormonal status, dietary habits, physical activity, among others). Ideally, the weight control should be accompanied by monitoring of complex patient profiles (family history, molecular profiles, medical imaging, etc.), in order to recommend healthy values optimized for the patient [11].
- Breast cancer is more frequent in *Jewish women* than in non-Jewish women and more frequent in black women than in Caucasian women. Women of Ashkenazi Jewish descent have a 1 in 40 (2.5%) risk of carrying a mutation in *BRCA1* and *BRCA2* genes, thus accounting for the increased risk in these women [11].
- *Diabetic history* is demonstrated as a risk factor for BC development and worse outcomes [16–18].
- *Metabolic syndrome* is characterized by increased levels of growth factors and inflammatory processes associated with BC development, progression, and poor outcomes [16].
- *Chronic inflammation* as a contributor and prognostic factor in BC: inflammatory processes are known to initiate and promote primary tumors and metastatic disease. In turn, obesity, metabolic syndrome with comorbidities, depression, hormonal stress, aging, as well as cancer therapy all are associated with systemic inflammation and BC risk [19].
- *Family history*: hereditary breast cancers account for 5–10% of all breast cancers and are thought to be attributable to highly penetrant inherited mutations in breast cancer susceptibility genes. Two such tumor suppressor genes, BRCA1 and BRCA2, have been well characterized. Carriers of germline mutations in

BRCA1/2 are predisposed to both breast and ovarian cancer types [20]: in case of these patient cohorts, an urgent need in predictive diagnostics is well justified for more effective preventive measures and targeted treatments. For women at high genetic risk due to a harmful mutation in BRCA1 or BRCA2, bilateral prophylactic mastectomy can reduce the risk of breast cancer by at least 95%. General predisposition to cancer consists of two major components: on the one side, a genetic (inherited) component, and on the other side, a cumulative effect of non-genetic risk factors (environmental, lifestyle, dietary habits, etc.). Consequently, the family history provides important information which may indicate inborn predisposition to cancer to be carefully considered for early screening, risk reduction strategies, and most effective treatments. Cancer (any type) history in the family may increase breast cancer risk for the next generations [21]. The cause of hereditary BC is the genetic component with the most common inherited mutations reported for BRCA1 and/or BRCA2 genes. Although in some BC-predisposed families with BRCA1/2 mutations, the lifetime risk may reach 80% and more, and the average risks range between 45 and 65%. This statistical data emphasize that the genetic component alone is not decisive enough for BC development: the crucial one is the individually managed interplay between genetic and non-genetic risk factors (environmental, lifestyle, dietary habits, etc.).

- *Use of diethylstilbestrol (DES)*
- *Increased breast density*

Environmental Factors

There is accumulating evidence that about 90% of cancers may be linked to environmental exposures [19, 22].

- Industrial air pollution [23]
- Toxic environmental contamination (heavy metals and genotoxic agents, etc.) [24]
- Ionizing radiation exposure (professional exposure, medical examinations, etc.) [25]
- Tobacco smoke (both active and passive) [26]
- Psychosocial stress factors (stressful interpersonal experience) [27]
- Viral infections (e.g., by mutagenic effects) [27]
- Professional occupation in specific branches (production of toxic compounds, higher-status occupation, rotating shift and night work, flight attendants, etc.) [28, 29]
- Risk factors for *male* breast cancer:
  - Obesity
  - Klinefelter syndrome (genetic condition)
  - Presence of excess breast tissue [11]

Protective Factors

- Long periods of *breastfeeding* have protective effects against breast malignancies.
- *Physical activity*: there are several attributes of physical inactivity with pronounced synergistic effects of cumulative breast cancer risk factors such as aging-related processes, overweight/obesity, altered insulin sensitivity, inflammation, and increased cytokine and estrogen production. In contrast, energy restriction is a well-known longevity contributor; further, regular physical activity reduces exposure to sex hormones [30], improves insulin sensitivity and immune and antioxidant defense capacity, and activates tumor suppressor genes [12, 31].

Staging

The American Joint Committee on Cancer (AJCC) determines staging of breast cancer using the tumor-node-metastasis system.
https://cancerstaging.org/references-tools/quickreferences/pages/default.aspx

Pathology

- Ductal carcinoma in situ.
- Paget's disease.
- Lobular carcinoma in situ.
- Invasive duct carcinoma *is the most common group of malignant mammary tumors and comprises 65–80% of all mammary carcinomas.*
- Infiltrating lobular carcinoma *constitutes 10–14% of invasive carcinomas.*
- Inflammatory carcinoma *is characterized by cutaneous findings present with an underlying invasive carcinoma.*
- Metastases from extramammary tumors.
- *Biologic markers and prognostic factors.*
- *Axillary lymph node status.*
- *Tumor size.*
- *Histologic grade.*
- *Molecular profiling.*
- *ERs/PRs: the hormone receptors can be measured by immunohistochemical (IHC) study positivity correlates with response to antihormonal agents and better prognosis.*
- HER2/neu is an oncogene overexpression or amplification that has been shown to correlate with a poor prognosis. Increased response to doxorubicin-based

therapy has been reported in the treatment of patients with positive nodes and overexpression of HER2/neu.
- *p53: accumulation of p53 protein has been reported to correlate with reduced survival in some studies* [11].

Screening

Screening for breast cancer is clearly indicated for all women at the appropriate age.

Current breast cancer screening programs utilize regular breast examination.

Determining a woman's unique risk factors will help to determine both the age at which that screening should begin and the intensity of that screening. It will also help to identify those women who need to be counseled regarding options for prevention of breast cancer. The hope is that by correctly identifying high-risk populations and then applying appropriate screening schedules and chemopreventive agents, many cases of breast cancers will be averted completely and that those that still occur will be found at the earliest stages. The role of the obstetrician and gynecologist in providing information on breast cancer diagnosis and screening is very important. In addition, the understanding of breast disease, both benign and malignant, is crucial not only in the diagnosis of disease but also in helping to guide women in their treatment and follow-up [11].

Mammograms and clinical breast exams are commonly used to screen for breast cancer [5].

Palpable Mass

Clinical breast examination and breast self-examination as methods for screening for breast cancer mainly aim at detection of palpable breast lesions. However, there are no published reports demonstrating these methods as being effective in breast cancer mortality risk reduction.

Mammography

Mammographic screening in women 40 years or older has reduced mortality by 20–30% [11]. The primary goal of mammography is to screen asymptomatic women to help detect breast cancer at an early stage. The goal of screening mammography is to find cancers before they are clinically palpable, more likely to be small, and less likely to have nodal involvement [11]. The effectiveness of screening also varies depending on the density of the breast. The greater the breast density, the lower the sensitivity of the mammography [11]. Mammographic screening in women 40 years or older has reduced mortality by 20–30% [11].

Mammographic Screening Interval

American Cancer Society (ACS) recommends a yearly mammogram starting at age 40, whereas the National Cancer Institute (NCI) recommends a mammogram every 1 or 2 years. ACOG recommendations on mammography are similar to the NCI guidelines [11].

Annual screening mammography may commence earlier than age 40 in a few special circumstances.

Breast Imaging Reporting and Data System (BI-RADS) 0–6
0 = incomplete
1 = negative and 6 = known biopsy proven malignancy

Diagnosis

Diagnostic Evaluation and Techniques

Palpable Mass

The workup of a patient with a dominant mass should include a bilateral mammogram.

Mammography

Some palpable cancers are invisible on mammography, so a negative study cannot always exclude cancer. It is important to note that the false-negative rate for mammograms is 10–15% and that a normal mammogram does not eliminate the need for further evaluation of a dominant mass in the breast. If the clinical examination is suspicious, a negative mammogram result should not delay further investigation [11].

Fine-Needle Aspiration or Biopsy

FNA can be extremely useful in providing a cytologic analysis of a palpable breast mass.

Needle Localization and Excision

Needle localization is a technique that allows surgical excision of a lesion that is non-palpable. The image guidance can be provided by mammogram, ultrasound, and in some cases MRI.

Image-Guided Percutaneous Breast Biopsy

With the current advancements available in breast imaging, percutaneous image-guided breast biopsy is increasingly being used as an alternative to surgical biopsy.

Stereotactic Biopsy

Stereotactic-guided core needle biopsy uses specialized mammography equipment to calculate the location of a lesion in three dimensions. Multiple tissue specimens are obtained for pathologic analysis. The procedure has a sensitivity of 70–100% and a specificity of 85–100%. Studies have shown 99% accuracy with a 14-gauge needle obtaining five specimens. Radiography should be performed routinely on women with specimens of breast microcalcifications to determine whether calcifications were obtained.

Ultrasound-Guided Biopsy

Surgical Excision/Breast Biopsy

The specimen should be adequately oriented for margin analysis by the pathologist and also sent for the appropriate markers such as estrogen receptor (ER) and progesterone receptor (PR) status and HER2/neu. Orientation of the specimen is important because a re-excision of a close or involved margin may need to be performed [11].

Breast Ultrasonography

This technique is used to distinguish between solid and cystic masses in the breast. It can be used to evaluate a focal mass identified on a mammogram or a palpable mass. It is also used as an adjuvant for biopsy. Because of its low specificity, it is not thought to be a good modality for screening. It cannot replace mammography because it has no ability to detect microcalcifications. Ultrasound can complement mammography in young women with dense breasts.

MRI

MRI has a high sensitivity in the diagnosis of breast cancer, ranging from 86 to 100%, but a low specificity, ranging from 37% to 97%. Because of this low specificity, it is of limited value in screening.

Current uses include evaluation of breast implants for rupture, evaluation of pectoralis involvement with extensive breast cancer, and evaluation of post-

lumpectomy bed fibrosis. Other uses include evaluation of occult breast cancers and evaluation of multifocal disease in those patients who are considering breast conservation.

There is greater sensitivity of MRI over the use of mammography alone in screening for breast cancer in high-risk women [11]. MRI has proved to be an extremely valuable tool in screening women at the highest risk for developing breast cancer. MRI is recommended for women with an approximately 20–25% or greater lifetime risk of developing breast cancer.

High-density breast tissue mammographic breast tissue density is crucial for increased breast cancer risk as well as false-negative and false-positive diagnoses [25].

BC risk for women with 70% or more density is estimated as being 4.64-fold higher compared to women with less than 5% density [32]. Examination utilizing magnetic resonance imaging is the first choice to be met in the case of high-density breast. Breast MRI screening in high-risk women under 40 yielded elevated cancer detection rates (11.7 per 1000) with no evidence of improvements in cancer detection rates by mammography. With a large majority of women under 40 demonstrating high levels of breast parenchymal density, the results suggest that MRI alone may be useful in screening high-risk women under 40 [33].

Treatment

Breast cancer treatment depends on the stage at diagnosis, the size and location of the tumor, and tumor characteristics. Most patients with intraductal carcinoma and stage I and stage II breast cancer have the options of breast conservation therapy and mastectomy. Those who have stage II or III disease at diagnosis may receive more aggressive treatment, which can result in greater likelihood and severity of the impact of treatment. For patients with invasive breast cancer, the axillary nodes can be addressed with a sentinel lymph node (SLN) biopsy and, possibly, an axillary dissection.

Treatment generally includes two key components—treatment of the breast that can include surgery (mastectomy or breast conservation therapy, sentinel lymph node biopsy, and local lymph nodes removal) either with or without radiation therapy (“local therapy”) and drug treatments for cancer cells that may have spread (“adjuvant systemic therapy”) outside the breast.

Local Therapy

Surgical treatment for breast cancer includes breast-conserving surgery with radiation or mastectomy with or without radiation and with or without immediate/delayed reconstruction. In women with a very high risk of contralateral cancer from

inherited susceptibility (e.g., patients with mutations in the breast and ovarian cancer susceptibility genes *BRCA1/BRCA2*), contralateral prophylactic mastectomy may be performed [5].

Systemic Therapy

Systemic therapy may precede ("neoadjuvant") or follow ("adjuvant") local therapy and consists of combinations of hormonal therapy, chemotherapy, and biologic agents [2].

The NCCN guidelines for chemotherapy are described in detail on the 2006 NCCN website (http://www.NCCN.org).

Node-Positive Breast Cancer

The Canadian consensus states that chemotherapy should be offered to all premenopausal women with stage II breast cancer. Polychemotherapy is preferred to prolonged single-agent therapy. A 6-month course of cyclophosphamide/methotrexate/5-fluorouracil (CMF) or a 3-month course of doxorubicin/cyclophosphamide (AC) was suggested.

Estrogen Receptor-Positive Breast Cancer

These patients with breast cancer would benefit from endocrine therapy.

Tamoxifen

Hormonal modulation with tamoxifen is recommended for patients with hormone receptor-positive disease, representing approximately 70% of breast cancers. Five years of tamoxifen treatment reduce recurrence risk by 47% and mortality by 26%; recent data suggest continuing tamoxifen for up to 10 years may also be beneficial [34, 35]. Despite these benefits, tamoxifen adherence is poor, particularly among young women [36–38]. Tamoxifen use reduces recurrence and mortality in women with ER-positive tumors, irrespective of age and menopausal status and whether the lymph nodes are positive or negative. There is no clear evidence of benefit in women with ER-poor tumors.

Aromatase Inhibitors

Aromatase inhibitors suppress estrogen levels by inactivating aromatase, the enzyme responsible for synthesizing estrogens from androgens. The American Society of Clinical Oncology now recommends aromatase inhibitors be used to lower the risk of recurrence in receptor-positive postmenopausal breast cancers as initial therapy or after treatment with tamoxifen. The duration of therapy has not yet been established.

Gene Expression Assays

Two gene-expression assays, used to determine the risk of breast cancer recurrence in patients with stage I or II node-negative breast cancer, are currently available.

Metastatic Disease

The goal of therapy in metastatic disease is palliation of symptoms because cure is unlikely. The majority of patients with metastatic disease receive antihormonal therapy. First-line agents include tamoxifen or aromatase inhibitors such as letrozole or anastrozole. These agents offer a 20% response with ER-/PR-positive tumors. Disease stabilization is the goal of therapy, and because these therapies are less toxic than chemotherapy, most patients will remain on them for prolonged periods. Chemotherapy is the next step.

Neoadjuvant Chemotherapy

Preoperative or neoadjuvant chemotherapy is attractive because it may reduce the amount of disease present and thereby facilitate obtaining clean surgical margins when the disease is still confined to the breast. This is often the case in inflammatory breast cancer.

Radiation Therapy

As discussed, radiation therapy is used in conjunction with lumpectomy for patients opting for breast conservation. Postmastectomy chest wall irradiation is used with increasing frequency. Women with a high risk of local recurrence will benefit from radiation therapy postmastectomy. Radiation therapy can also be used in the palliative setting. It can be used for metastatic lesions to the bone or brain and can help to alleviate the patient's symptoms.

Breast Reconstruction

Breast reconstruction represents a major advance in cancer rehabilitation for patients undergoing a mastectomy.

There is no standardized follow-up model for patients with early-stage breast cancer who have completed surgery, chemotherapy, and radiation. Most of these women will have endocrine-responsive tumors and will require endocrine therapy for a total of 5–10 years [2].

Breast cancer survivors face potentially significant impacts of cancer and its treatment and deserve high-quality, comprehensive, coordinated clinical follow-up care. Primary care clinicians must consider each patient's individual risk profile and preferences of care to address physical and psychosocial impacts [2].

- Body image concerns
- Lymphedema
- Cardiotoxicity
- Cognitive impairment
- Distress, depression, and anxiety
- Fatigue
- Bone health
- Musculoskeletal health
- Pain and neuropathy
- Sexual health
- Effect on fertility

Effect on Fertility

One of the most characteristic features of hereditary breast cancer is its tendency to manifest at a young age. In the Breast Cancer Consortium's study of *BRCA1*-linked families that transmit *BRCA1* mutations, more than 80% of breast cancers occurred in women younger than 50 years of age [11].

Breast cancer is the most frequently occurring cancer in women of reproductive age, and findings have shown systemic regimens to be gonadotoxic [39], with possible causation of temporary or permanent amenorrhea, premature menopause [40], and infertility; this may adversely affect childbearing plans [1]. The use of assisted reproductive technologies and therapies for ovarian protection improves fertility prospects [9].

Breast cancer in young women is generally known to have more aggressive tumor biology [41]; however, with advancing systemic treatments, the National Cancer Institute estimates that, overall, breast cancer patients under the age of 45 years have a promising 5-year survival rate of 92%. Survivors face undesirable

consequences of adjuvant cytotoxic and endocrine therapy [10, 42], which, in young women, includes impairment of ovarian function, a side effect that is especially important in those who desire future childbearing; many young BC patients have not yet completed their families at the time of diagnosis. Chemotherapy treatment is shown to cause chemotherapy-induced amenorrhea (CIA) in 21–70% of women under the age of 40 years [43]. Additionally, for women with estrogen receptor (ER)-positive breast cancer, the use of adjuvant hormone therapy is typically recommended for a period of 5–10 years after diagnosis [35], and pregnancy is a contraindication during treatment because of teratogenic effects [44]. This further delays childbearing plans in women who may have diminished ovarian reserve due to their gonadotoxic treatments [3, 9].

It is considered that less than 10% of women treated for invasive BC under age of 40 have children post-diagnosis [45–47]. The reproductive potential of survivors has become a major concern since 50% of young cancer patients report a desire for pregnancy [3, 48].

Systemic Therapy and Effect on Reproductive System

The risk of chemotherapy-related amenorrhea (CRA) directly correlates with cyclophosphamide dose, because alkylating agents are particularly gonadotoxic [49, 50]. Hence, CMF causes significantly higher rates of CRA than AC [51]. The gonadotoxic effect of taxanes is unclear. Gonadotoxicity of platinum agents should also be a priority, given recent evidence that platinum compounds are particularly effective in *BRCA1-/BRCA*2-mutated patients [17]. Of relevance to HER2-positive patients, available data suggest no significant additive impact on amenorrhea from 1 year of trastuzumab therapy [12, 51, 52]. In women treated for hormone receptor-positive early-stage breast cancer, multiple studies demonstrate an association between tamoxifen use and persistence of postchemotherapy [51] amenorrhea [52–54]. Rather than representing a gonadotoxic effect of tamoxifen, this likely reflects the known association of tamoxifen with menstrual irregularities, in addition to the natural age-related loss in ovarian reserve that occurs over a standard 5- to 10-year course of tamoxifen [51].

Fertility Preservation

*F*ertility preservation is a central element of survivorship for many of the more than 25,000 reproductive-aged women diagnosed with breast cancer each year [1]. With approximately 15% of diagnoses occurring in women of reproductive age, breast cancer is the most common malignancy diagnosed in this age subset [51, 55, 56]. Given the increasing population of young women, the trend for women in our society to delay childbearing until later in life [55, 57] and ongoing improvements in breast cancer survival, the population of women who desire pregnancy after a breast cancer diagnosis is increasing [51]. Premenopausal patients should be asked of their desire for future fertility and be informed of the effects of chemotherapy; those who desire pregnancy should be referred to a fertility specialist for consultation [9]. Over the last decade, the demand for fertility preservation (FP) has dramatically increased and now represents a standard of care for young patients having to undergo gonadotoxic cancer treatment [3, 58].

Beyond additional choices of adoption and oocyte donation, improvements in assisted reproductive technologies (ART) have allowed options for women to undergo fertility preservation prior to initiation of chemotherapy. Specifically, embryo or oocyte cryopreservation (oocytes are frozen before fertilization) [51]

after a protocol of controlled ovarian stimulation using exogenous hormones to achieve ovarian follicle maturation [3, 58] are currently the gold standard option for fertility preservation in young women with cancer. These methods have shown a live birth rate of 40% for oocytes and 50% for embryos [9]. One of the concerns associated with both of these methods is the need to delay cancer treatment. Part of the need for this delay, which is usually only a few weeks, arises from the standard practice of waiting to begin ovarian stimulation until the follicular phase of the menstrual cycle. In addition, a growing number of young BC patients are candidates for urgent neoadjuvant chemotherapy, preceding surgery [59], and this significantly complicates FP attempts, since the window for optimal preservation between diagnosis and initiation of gonadotoxic treatment is dramatically narrowed and the tumor is still in place during follicle stimulation [3]. Recent data suggest that the number of aspirated oocytes and the oocyte fertilization rate obtained after stimulation starting in the standard follicular phase versus the nonstandard luteal phase of the cycle are not significantly different, indicating that both phases may be viable options [25]. The risk of supraphysiologic serum estradiol levels reached after ovarian stimulation should be considered in hormone-sensitive tumors such as BC, even when the FP procedures are performed after surgical removal of the tumor and before adjuvant chemotherapy [51].

Recently, retrieval of cumulus-oocyte complexes (COCs) from small antral follicles, without exogenous FSH administration, has been proposed as an option for young patients seeking FP, in particular when controlled ovarian hyperstimulation is unfeasible or unsuitable [60]. Indeed, after in vitro maturation (IVM), the metaphase II oocytes may be frozen or fertilized for embryo cryopreservation. Although the clinical efficiency of this procedure remains hard to assess at present, it may constitute the safer option for patients wishing oocyte cryopreservation before breast tumorectomy. In addition, IVM can be combined with ovarian tissue cryopreservation (this process involves surgical oophorectomy and cryopreservation of ovarian cortical strips before chemotherapy) to cumulate FP strategies [3, 60]. Whatever the technique used (i.e., ovarian stimulation or IVM) and the timing of either the initiation of exogenous gonadotrophin administration or immature oocyte retrieval (i.e., follicular or luteal phase), very few live births have been reported in these women [61–63]. Caution should be taken before concluding to the same efficiency of IVM performed during the follicular or the luteal phase [3]. Investigation shows that the retrieval of immature oocytes from small antral follicles as well as the IVM rates remains similar whatever the period of the menstrual cycle these data suggest that IVM can be offered to BC patients seeking urgent FP [3].

Regarding the ovarian tissue cryopreservation which is thawed and transplanted back into the host in an autologous fashion, the main risk of this technique is the potential to transplant malignant cells back into the body along with ovarian tissue, although this has never been reported, and multiple histologic and microscopic screening measures to minimize this risk are available [58, 64]. Both of these ovarian cryopreservation-based techniques remain investigational and are not generally available to patients with breast cancer outside of a clinical trial [58].

A final potential fertility preservation strategy, and a topic of much debate, is the use of gonadotropin-releasing hormone (GnRH) agonists concurrent with chemotherapy. The use of GnRH agonists has been posited to improve the chances of ovarian recovery postchemotherapy through a variety of mechanisms, including decreasing ovarian and uterine perfusion, increasing antiapoptotic mechanisms within the ovary, and protecting germline stem cells [20]. Increasing data support the use of GnRH agonists for ovarian protection; it is important to note that the overall body of evidence remains inconsistent [51]. In a recent randomized controlled trial, a gonadotropin-releasing hormone (GnRH) agonist administered during chemotherapy was found to reduce the rate of ovarian failure from 22% to 8% and improve the prospects for subsequent fertility.

Health-related concerns, including fear of future cancer recurrence or treatment-related complications, anxiety about treatment delay, [44]; and fear about the safety of future pregnancy, all, may heighten apprehension about fertility preservation at the time of diagnosis. It has been demonstrated that pregnancy after breast cancer confers no increased risk of adverse outcomes [45, 46]. In fact, pregnancy after breast cancer is associated with improved survival [47, 51].

References

1. Goldfarb SB, Kamer SA, Oppong BA, Eaton A, Patil S, Junqueira MJ, et al. Fertility preservation for the young breast cancer patient. Ann Surg Oncol. 2016;23(5):1530–6.
2. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34(6):611–35.
3. Grynberg M, Poulain M, le Parco S, Sifer C, Fanchin R, Frydman N. Similar in vitro maturation rates of oocytes retrieved during the follicular or luteal phase offer flexible options for urgent fertility preservation in breast cancer patients. Hum Reprod. 2016;31(3):623–9.
4. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.
5. A Snapshot of Breast Cancer National Cancer Institute: NIH. 2014. Available from: http://www.cancer.gov/research/progress/snapshots/breast.
6. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973-1997. Int J Epidemiol. 2005;34(2):405–12.
7. Howlader N, Chen VW, Ries LA, Loch MM, Lee R, DeSantis C, et al. Overview of breast cancer collaborative stage data items – their definitions, quality, usage, and clinical implications: a review of SEER data for 2004-2010. Cancer. 2014;120(Suppl 23):3771–80.
8. A Snapshot of Adolescent and Young Adult Cancers National Institute of Health: National Cancer Institute. 2014. Available from: http://www.cancer.gov/research/progress/snapshots/adolescent-young-adult.
9. McCray DK, Simpson AB, Flykct R, Liu Y, O'Rourke C, Crowe JP, et al. Fertility in women of reproductive age after breast cancer treatment: practice patterns and outcomes. Ann Surg Oncol. 2016;23(10):3175–81.
10. Akduman AT, Ozerkan K, Zik B, Peker S, Avci B, Ata B. Effect of tamoxifen on ovarian reserve: a randomized controlled assessor-blind trial in a mouse model. J Turk German Gynecol Assoc. 2014;15(4):228–32.

11. Gemignani ML. Breast diseases. In: Di Saia PJ, editor. Clinical gynecologic oncology. 1st ed. Philadelphia: Elsevier/Saunders; 2012. p. 369–403.
12. Golubnitschaja O, Debald M, Yeghiazaryan K, Kuhn W, Pesta M, Costigliola V, et al. Breast cancer epidemic in the early twenty-first century: evaluation of risk factors, cumulative questionnaires and recommendations for preventive measures. Tumour Biol J Inter Soc Oncodev Biol Med. 2016;37(10):12941–57.
13. Colditz GA, Bohlke K, Berkey CS. Breast cancer risk accumulation starts early: prevention must also. Breast Cancer Res Treat. 2014;145(3):567–79.
14. Liu Y, Colditz GA, Rosner B, Berkey CS, Collins LC, Schnitt SJ, et al. Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. J Natl Cancer Inst. 2013;105(20):1571–8.
15. Johansson H, Bonanni B, Gandini S, Guerrieri-Gonzaga A, Cazzaniga M, Serrano D, et al. Circulating hormones and breast cancer risk in premenopausal women: a randomized trial of low-dose tamoxifen and fenretinide. Breast Cancer Res Treat. 2013;142(3):569–78.
16. Boyle P, Boniol M, Koechlin A, Robertson C, Valentini F, Coppens K, et al. Diabetes and breast cancer risk: a meta-analysis. Br J Cancer. 2012;107(9):1608–17.
17. Wu AH, Kurian AW, Kwan ML, John EM, Lu Y, Keegan TH, et al. Diabetes and other comorbidities in breast cancer survival by race/ethnicity: the California Breast Cancer Survivorship Consortium (CBCSC). Cancer Epidemiol Biomarkers Prev Pub Am Asso Cancer Res Cosponsored Am Soc Prev Oncol. 2015;24(2):361–8.
18. Cebioglu M, Schild HH, Golubnitschaja O. Cancer predisposition in diabetics: risk factors considered for predictive diagnostics and targeted preventive measures. EPMA J. 2010;1(1):130–7.
19. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883–99.
20. Randall TC, Armstrong K. Health care disparities in hereditary ovarian cancer: are we reaching the underserved population? Curr Treat Options in Oncol. 2016;17(8):39.
21. Rubinstein WS, Acheson LS, O'Neill SM, Ruffin MT, Wang C, Beaumont JL, et al. Clinical utility of family history for cancer screening and referral in primary care: a report from the Family Healthware Impact Trial. Genet Med Off J Am Coll Med Genetic. 2011;13(11):956–65.
22. Heikkila K, Nyberg ST, Theorell T, Fransson EI, Alfredsson L, Bjorner JB, et al. Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116,000 European men and women. BMJ (Clinical Res ed). 2013;346:f165.
23. Fazzo L, Carere M, Tisano F, Bruno C, Cernigliaro A, Cicero MR, et al. Cancer incidence in Priolo, Sicily: a spatial approach for estimation of industrial air pollution impact. Geospat Health. 2016;11(1):320.
24. Zimeri AM, Robb SW, Hassan SM, Hire RR, Davis MB. Assessing heavy metal and PCB exposure from tap water by measuring levels in plasma from sporadic breast cancer patients, a pilot study. Int J Environ Res Public Health. 2015;12(12):15683–91.
25. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. Br J Cancer. 2013;108(11):2205–40.
26. White AJ, Bradshaw PT, Herring AH, Teitelbaum SL, Beyea J, Stellman SD, et al. Exposure to multiple sources of polycyclic aromatic hydrocarbons and breast cancer incidence. Environ Int. 2016;89–90:185–92.
27. Williams DR, Mohammed SA, Shields AE. Understanding and effectively addressing breast cancer in African American women: unpacking the social context. Cancer. 2016;122(14):2138–49.
28. Monsees GM, Kraft P, Hankinson SE, Hunter DJ, Schernhammer ES. Circadian genes and breast cancer susceptibility in rotating shift workers. Int J Cancer. 2012;131(11):2547–52.
29. Rafnsson V, Tulinius H, Jonasson JG, Hrafnkelsson J. Risk of breast cancer in female flight attendants: a population-based study (Iceland). Cancer Causes Control CCC. 2001;12(2):95–101.

30. Bernstein L. Exercise and breast cancer prevention. Curr Oncol Rep. 2009;11(6):490–6.
31. Ballard-Barbash R, Hunsberger S, Alciati MH, Blair SN, Goodwin PJ, McTiernan A, et al. Physical activity, weight control, and breast cancer risk and survival: clinical trial rationale and design considerations. J Natl Cancer Inst. 2009;101(9):630–43.
32. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev Pub Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2006;15(6):1159–69.
33. Narayan AK, Visvanathan K, Harvey SC. Comparative effectiveness of breast MRI and mammography in screening young women with elevated risk of developing breast cancer: a retrospective cohort study. Breast Cancer Res Treat. 2016;158(3):583–9.
34. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet (London, England). 1998;351(9114):1451–67.
35. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet (London, England). 2013;381(9869):805–16.
36. Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2003;21(4):602–6.
37. Hershman DL, Kushi LH, Shao T, Buono D, Kershenbaum A, Tsai WY, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(27):4120–8.
38. Barron TI, Connolly R, Bennett K, Feely J, Kennedy MJ. Early discontinuation of tamoxifen: a lesson for oncologists. Cancer. 2007;109(5):832–9.
39. Ben-Aharon I, Shalgi R. What lies behind chemotherapy-induced ovarian toxicity? Reproduction (Cambridge, England). 2012;144(2):153–63.
40. Tham YL, Sexton K, Weiss H, Elledge R, Friedman LC, Kramer R. The rates of chemotherapy-induced amenorrhea in patients treated with adjuvant doxorubicin and cyclophosphamide followed by a taxane. Am J Clin Oncol. 2007;30(2):126–32.
41. Bao T, Davidson NE. Gene expression profiling of breast cancer. Adv Surg. 2008;42:249–60.
42. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 1996;14(5):1718–29.
43. Minton SE, Munster PN. Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. Cancer Contr J Moffitt Cancer Center. 2002;9(6):466–72.
44. Cunha GR, Taguchi O, Namikawa R, Nishizuka Y, Robboy SJ. Teratogenic effects of clomiphene, tamoxifen, and diethylstilbestrol on the developing human female genital tract. Hum Pathol. 1987;18(11):1132–43.
45. Mueller BA, Simon MS, Deapen D, Kamineni A, Malone KE, Daling JR. Childbearing and survival after breast carcinoma in young women. Cancer. 2003;98(6):1131–40.
46. Blakely LJ, Buzdar AU, Lozada JA, Shullaih SA, Hoy E, Smith TL, et al. Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. Cancer. 2004;100(3):465–9.
47. Cvancarova M, Samuelsen SO, Magelssen H, Fossa SD. Reproduction rates after cancer treatment: experience from the Norwegian radium hospital. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(3):334–43.
48. Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2004;22(20):4174–83.
49. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, et al. Impact of cancer therapies on ovarian reserve. Fertility Sterility. 2012;97(1):134–40.e1.

50. Torino F, Barnabei A, De Vecchis L, Sini V, Schittulli F, Marchetti P, et al. Chemotherapy-induced ovarian toxicity in patients affected by endocrine-responsive early breast cancer. Crit Rev Oncol Hematol. 2014;89(1):27–42.
51. Waks AG, Partridge AH. Fertility preservation in patients with breast cancer: necessity, methods, and safety. J Nat Compr Cancer Network JNCCN. 2016;14(3):355–63.
52. Abusief ME, Missmer SA, Ginsburg ES, Weeks JC, Partridge AH. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. Cancer. 2010;116(4):791–8.
53. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol Off J Am Soc Clin Oncol. 1999;17(8):2365–70.
54. Blumenfeld Z. Preservation of ovarian function and minimizing premature ovarian failure during chemotherapy using gonadotropin-releasing hormone analogs. Women's Health (London, England). 2011;7(6):635–40.
55. Oktay K, Turan V, Bedoschi G, Pacheco FS, Moy F. Fertility preservation success subsequent to concurrent aromatase inhibitor treatment and ovarian stimulation in women with breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(22):2424–9.
56. Shapira M, Raanani H, Meirow D. IVF for fertility preservation in breast cancer patients – efficacy and safety issues. J Assist Reprod Genet. 2015;32(8):1171–8.
57. Rosenberg SM, Newman LA, Partridge AH. Breast cancer in young women: rare disease or public health problem? JAMA Oncology. 2015;1(7):877–8.
58. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(19):2500–10.
59. Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(12):1940–9.
60. Berwanger AL, Finet A, El Hachem H, le Parco S, Hesters L, Grynberg M. New trends in female fertility preservation: in vitro maturation of oocytes. Future Oncol (London, England). 2012;8(12):1567–73.
61. Porcu E, Venturoli S, Damiano G, Ciotti PM, Notarangelo L, Paradisi R, et al. Healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer. Reprod BioMed Online. 2008;17(2):265–7.
62. Kim MK, Lee DR, Han JE, Kim YS, Lee WS, Won HJ, et al. Live birth with vitrified-warmed oocytes of a chronic myeloid leukemia patient nine years after allogenic bone marrow transplantation. J Assist Reprod Genet. 2011;28(12):1167–70.
63. Prasath EB, Chan ML, Wong WH, Lim CJ, Tharmalingam MD, Hendricks M, et al. First pregnancy and live birth resulting from cryopreserved embryos obtained from in vitro matured oocytes after oophorectomy in an ovarian cancer patient. Hum Reprod. 2014;29(2):276–8.
64. Salama M, Woodruff TK. New advances in ovarian autotransplantation to restore fertility in cancer patients. Cancer Metastasis Rev. 2015;34(4):807–22.

Chapter 17
Ovarian Cancer

Definition

Malignant neoplasms of the ovary are the cause of more deaths than any other female genital tract cancer [1]. The majority (85–90%) of malignant ovarian tumors are epithelial [2, 3], and about 10% are germ cell (more frequent among young women and adolescents) and sex cord–stromal tumors (OSCST) [4].

The classification of ovarian epithelial tumors differentiates them into benign, borderline ovarian tumors (BOT), and malignant tumors (10%) and according to whether adenomatous or fibrous elements are dominant [4].

They can be grouped into predominant histological types as follows [1]:

Serous cystadenocarcinoma	42%
Mucinous cystadenocarcinoma	12%
Endometrioid carcinoma	15%
Undifferentiated carcinoma	17%
Clear cell carcinoma	6%

Incidence, Epidemiology, and Etiology

Incidence and Mortality

Ovarian cancer accounts for approximately 3% of all cancers in women, and it is the fifth leading cause of cancer-related death among women in the United States [1, 5] and causes more deaths than any other female reproductive system cancer. It is the second most common gynecologic cancer accounting for 26–27% of tumors but

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_17

52–53% of the total mortality [1, 4], a leading cause of cancer-related death in the Unites States [2, 6]. It causes more than 140,000 deaths each year worldwide [7, 8].

Ovarian cancer incidence rates declined by nearly 1% annually from 1987 to 2011; mortality rates fell an average of 1.6% each year from 2001 to 2010 [5].

White women have higher incidence and mortality rates than women of other racial/ethnic groups. Over the past 30 years, mortality rates have decreased for women younger than 65 years, whereas rates increased for women older than 65 years, with some plateauing over the past 10 years. These changes may result from increased use of oral contraceptives in younger patients [5]. There is also a substantial geographic variation in its prevalence [2, 9, 10]. Malignant neoplasms of the ovaries occur at all ages, women of childbearing age, infancy, and childhood. Survival is worse in older women. Some have suggested this may be a result of less aggressive treatment in the older woman and the higher percentage of low-grade disease in younger patients. Throughout childhood and adolescence, the rate of death from ovarian carcinoma in the United States is exceeded by those for leukemia, lymphomas, and neoplasms of the central nervous system, kidney, connective tissue, and bone. The major histological types occur in distinctive age ranges. Malignant germ cell tumors (OGCT) are most commonly seen in girls younger than age 20 years, whereas epithelial cancers of the ovary are primarily seen in women older than age 50 years [1]. Elderly women are more likely than younger women to be in advanced stages of ovarian cancer at initial diagnosis.

Several reports have estimated that 3–17% of all epithelial ovarian cancer occur in women younger than 40 years of age [10]. According to the 25th FIGO Annual Report, 14.4% of epithelial ovarian cancer patients were younger than 40 [11]. Borderline and early-stage invasive disease seems to be more frequent in women of childbearing age [4, 5].

Risk Factors

A number of epidemiological risk factors are associated with ovarian cancer.

- Early menarche
- Late menopause
- Low parity
- Infertility
- Family history
- Use of estrogen-only hormone replacement therapy
- Use of fertility drugs
- Use of talc
- Obesity
- Tall height [5]

Other factors such as galactose consumption, smoking, or childhood viruses have not been strongly correlated with epithelial ovarian cancer [4].

Etiology

Environmental factors are major etiologic determinants in epithelial cancer of the human ovary. All these factors, taken together, have led to the hypothesis that "incessant ovulation" (through repeated stimulation of the epithelium of the ovarian surface) may be an important factor in pathogenesis of ovarian cancer, predisposing the epithelium to malignant transformation [12] which in turn can act as a promoting factor in the carcinogenic process [1]. Multiple lines of evidence suggest that ovarian cancer may be related to chronic inflammation [13]. In addition to inflammatory factors associated with ovarian epithelial disruption through ovulation [14, 15], inflammation-related exposures such as endometriosis [16–18] and exposure to talc or genital powder and asbestos [19] have been associated with increased ovarian cancer risk [7].

Whittemore and others [20] have shown that the odds for invasive epithelial ovarian cancer vary with the number of term pregnancies each woman experiences. Danforth et al. [21] prospectively examined risk of ovarian cancer in the Nurses' Health Studies and found that women who never breastfed faced a 1.5-fold risk of ovarian cancer compared with women who breastfed for greater than 18 months. These observations coincided with data that shows a reduction in the disease incidence with the use of oral contraceptives [1].

The published data suggest that there is probably little relationship between fertility drug use and ovarian cancer. Nulliparity and certain causes of infertility (e.g., endometriosis) are factors associated with an increased risk of ovarian cancer [8]. The use of fertility treatment has grown substantially in recent decades, with ovulation-inducing drugs. An association between ovulation-inducing drugs and ovarian cancer risk is biologically plausible, given that the most commonly used medications, clomiphene citrate (CC) and gonadotropins, are effective at stimulating ovulation. Clomiphene citrate induces ovulation indirectly; it is a first-line treatment for women with anovulatory infertility and is also used for ovulatory women with unexplained infertility. Gonadotropins stimulate ovulation directly through follicular recruitment and induced folliculogenesis. An increased risk of ovarian cancer with ovulation-inducing drug use was suggested in two early studies [22, 23], whereas recent cohort studies among infertile women suggest no association [13–16, 24–26].

Concerns persist among certain subgroups of women who remain nulligravid despite ovulation-inducing drug use [17–19, 22], increased risk with extended follow-up [18], and increased risk of borderline ovarian tumors [15, 17, 23]. Overall findings were generally reassuring in not confirming a link between use of ovulation-inducing drugs and risk of subsequent ovarian cancer. In comparisons with other infertile women, there was no evidence that use of either CC or gonadotropins was associated with a substantial risk of ovarian cancer. However, other study does suggest that ovarian cancer risk is increased among women with resistant infertility (those who remained nulligravid), supporting the need for longer follow-up of existing cohorts and additional studies to evaluate long-term effects on ovarian cancer risk [7].

Factors associated with a reduced risk (protection against ovarian cancer):

- Oral contraceptive use.
- Pregnancy.
- Lactation.
- Using acetaminophen daily had a death rate from ovarian cancer 45% lower than that of women reporting no use [1]. An analysis of pooled data from 12 case-control studies found that women who took aspirin regularly had a 20–34% lower risk of ovarian cancer than those who did not, with the greatest risk reduction in women who took aspirin daily and who took low-dose aspirin [27].

Increasing parity: this could be explained thinking that the endocrinologic status of pregnancy protects against ovarian cancer and that the lack of this protection places infertile women at higher risk for ovarian cancer or it could be that infertility and ovarian cancer result from the same abnormal gonadal status [1].

Hereditary Ovarian Cancer

Site-specific familial ovarian cancer

1. Breast-ovarian cancer syndrome, in which there is an increased incidence of breast and ovarian carcinomas alone or in combination. True hereditary ovarian cancer and breast cancer mainly result from mutations of BRCA1 and BRCA2 genes. Individuals with these mutations generally have a germline mutation (inherited mutated copy of the gene) in contrast to the more common somatic mutation (non-inherited or acquired) in most patients with ovarian cancer. Inherited genetic mutations are associated with approximately 10% of women who develop ovarian cancer. The mutation is inherited in an autosomal-dominant fashion (maternal or paternal transmission), and multiple family members are affected over several generations. First-degree relatives (mother or sister) are frequently involved. However, in most women with a strong family history who do develop ovarian cancer, the disease is sporadic in nature and not inherited. The estimated risk of ovarian cancer is of 32–84% for carriers of the BRCA1 mutation and much lower rate for carriers of the BRCA2 mutation. A family history of breast or ovarian cancer, particularly before the age of 50 years in a first-order relative, and Ashkenazi Jewish ancestry are risk factors for BRCA1 or BRCA2 mutations. Family history, both maternal and paternal, should be obtained (three generations is desired), and age at diagnosis should be noted [1].
2. A second familial disorder that carries with it an increased risk of ovarian cancer is Lynch syndrome type II. In patients with this syndrome, family members may develop a variety of cancers, including colorectal, endometrial, and ovarian cancer. Lynch II syndrome is a result of inherited mutation in a family of DNA repair genes (MSH2, MLH1, PMS1, PMS2); this group accounts for only a small number of inherited ovarian cancers. Affected families have a predominance

of hereditary non-polyposis colon cancer, often on the right side of the colon and sometimes in association with other cancers, such as those of the endometrium, ovaries, or genitourinary tract [5].

If a suspect mutation is found in the cancer member, the relatives without cancer should be tested for that specific mutation [1].

There is a family history in between 5% and 10% of women with epithelial ovarian cancers. These women have a higher risk of ovarian cancer than the general population. A woman with two first-degree relatives with breast or ovarian cancer has a lifetime risk of 30–40%. Hereditary ovarian cancers generally occur in women about 10 years younger than nonhereditary tumors [4]. Women who are known to have an increased risk of ovarian cancer due to genetic mutations but no signs of the disease may consider risk-reducing surgery to remove the ovaries and fallopian tubes [5].

Diagnosis

Most ovarian neoplasms grow quickly and painlessly [7]. Although early-stage ovarian cancer can be successfully treated, the high mortality rate reflects, in part, a lack of early symptoms and a lack of effective screening tests [1], and the disease is commonly detected at advanced stages with extensive local and systemic spread and poor survival [1].

Primary prevention strategies have not been widely studied but may present alternatives to reduce ovarian cancer burden. Methods for early diagnosis or screening have been investigated using cul-de-sac aspiration for peritoneal cytologic assessment, frequent pelvic examinations, transvaginal ultrasonography, and biomarkers; these had been insufficient to improve early detection efforts so far [7, 24, 25]. All these have failed to show a significant impact on early diagnosis of this disease and have not been shown to reduce mortality [7, 22, 23]. Currently there are no reliable data that screening for ovarian cancer is effective in improving length and quality of life in these patients. Pelvic examination remains the most practical means of detecting early disease [1].

Clinical Manifestations

Symptoms ordered by relative frequency:

- Abdominal swelling
- Abdominal pain: usually a late complication; it is seen with early disease only in association with a complication such as torsion, rupture, or, rarely, infection [1].
- Dyspepsia
- Urinary frequency
- Weight change

Findings in the ultrasound and surgery will give us an idea of the nature of the disease (benign or malignant), and the diagnosis rests with the histologic examination of the specimen.

Elements of Benign disease:
- Totally cystic
- Intact capsule
- Unilateral

Elements of malignant disease:
- Surface papilla
- Intracystic papillary solid areas
- Bilaterality
- Adhesions
- Ascites (100 ml)
- Necrosis
- Peritoneal implants

The size of the tumor does not indicate the severity of disease; many of the largest neoplasms are histologically benign, most commonly mucinous cystadenoma.

Serological Biomarkers: CA 125

Less than 50% of patients with stage I ovarian cancer will have an elevated CA 125 concentration, and this can be elevated by benign and malignant conditions.

Ultrasound

Ultrasound examination findings that may suggest malignant disease are complex mass, >5 cm, or intracystic papillations.

For premenopausal women with a suspicious pelvic mass, referral to a gynecologic oncologist should be considered by at least one of the following:

- CA 125 level higher than 200 U/Ml
- Ascites
- Abdominal or distant metastases
- One or more first-degree relatives with breast or ovarian cancer

Surgical exploration is the ultimate test as to the nature of the disorder.

Differential Diagnosis

Non-ovarian causes of apparent adnexal masses are:

- Diverticulitis

- Tubo-ovarian abscess
- Carcinoma of the cecum or sigmoid
- Pelvic kidney
- Uterine or intraligamentous myomas

Staging

The staging of ovarian cancer is surgical and based on the surgical and pathologic findings. Proper staging is important for treatment planning, clinical decision-making regarding type and duration of adjuvant therapy, and providing an accurate prognosis.

Survival Is Affected by

- Cancer stage
- Grade of differentiation
- Findings at surgery
- Amount of residual tumor after surgery
- Additional treatment required

Guidelines for Staging in Epithelial Ovarian Cancer

- Four peritoneal washings (diaphragm, right and left abdomen, pelvis)
- Careful inspection and palpation of all peritoneal surfaces
- Biopsy or smear from undersurface of right hemidiaphragm
- Biopsy of all suspicious lesions
- Infracolic omentectomy
- Biopsy or resection of any adhesions
- Random biopsy of normal peritoneum of bladder reflection cul-de-sac, right and left paracolic recesses, and both pelvic sidewalls (in the absence of obvious implants)
- Selected lymphadenectomy of pelvic and para-aortic nodes

Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and excision of masses when prudent

Staging Classification Using the FIGO Nomenclature (Links)

http://www.figo.org/figo-cancer-report-20122015

http://www.ijgo.org/article/S0020-7292(15)00378-1/abstract

http://www.ncbi.nlm.nih.gov.ezproxy.galter.northwestern.edu/pubmed/27042752

Treatment

Standard treatments for ovarian cancer include surgery, radiation therapy, and chemotherapy [5]. The standard surgical management of epithelial ovarian cancer includes total hysterectomy and bilateral salpingo-oophorectomy [2, 28].

Surgical Therapy in Ovarian Cancer

- Peritoneal cytologic examination
- Determination of extent of disease: pelvis, peritoneal surfaces, diaphragm, omentum, and lymph nodes (lymphadenectomy is an important diagnostic and therapeutic procedure)
- Removal of all tumor possible (total abdominal hysterectomy and bilateral salpingo-oophorectomy) plus node sampling and omentectomy

In the management of *stage I* ovarian cancer, the physician must weigh the possible benefits of adjuvant chemotherapy against the risks. It appears reasonable to not recommend adjuvant therapy for patients with stage IA, IB, grade I, and II lesions who have been comprehensively staged. Pelvic and aortic lymph nodes may be involved 10–20% of the time in apparent stage I disease. Patients with stage I, grade III, and stage IC disease present a more difficult problem because the incidence of recurrence in this group approaches 50% in some series.

The therapy of choice for *stage IIA* and *stage IIB* disease is staging surgery followed by platinum-based combination chemotherapy.

In *stage III*, as in other stages, every effort should be made to remove the uterus with both adnexa. In addition, every reasonable effort should be made to remove all visible ovarian tumors. Retrospective studies have strongly suggested that the survival rate in patients with stage III disease is related to the amount of residual tumor after surgery, such that patients with no macroscopic ($\leq$2 cm) residual tumor appear to have the best prognosis after primary chemotherapy, a suboptimal surgery would leave a residual tumor $\geq$2 cm. Most centers prefer combination platinum-based chemotherapy, usually carboplatin and paclitaxel, for this group of patients, and because of the excellent response rates reported in the literature, platinum-based combinations have proved to be the most successful [1]. There is also an option of doing neoadjuvant chemotherapy before surgery.

The ideal management of *stage IV* disease is to remove as much cancer as possible and to administer chemotherapy after surgery.

The goal of primary surgery for advanced ovarian cancer should be to remove all visible tumors. The most important factors proved to be histologic grade of the tumor and size of the largest residual mass after primary surgery.

Radiation therapy as a second-line treatment in patients with chemotherapy-persistent or recurrent ovarian cancer has its advocates.

If a woman was undergoing pelvic surgery, removal of the ovaries at that time would almost fully eliminate her risk of ovarian cancer (although there remains a small risk of peritoneal cancer). If the woman is premenopausal, discussion of estrogen replacement therapy is important before removal of the ovaries because for some younger women, if estrogen replacement is not used, the risk of premature menopause and the potential for osteoporosis may outweigh the risk of ovarian conservation and the potential for ovarian cancer [1].

Borderline Malignant Epithelial Neoplasms

Definition, Incidence, and Epidemiology

Borderline malignant neoplasms (BOT) account for approximately 15% of all epithelial ovarian cancers, having an incidence of 1.8–4.8 out of 100,000 women per year, and are typically indolent neoplasms; these tumors may have a 10-year survival rate approaching 95% [29–33]. These tumors have also been called proliferative cystadenomas and tumors of low malignant potential. BOTs are a disease of younger, fertile women, with generally a benign course [34]. Median age at diagnosis is 40–55 years in different reports [33, 35–37]; a minority of patients present at an advanced stage and even those who do may expect extended survival [32, 33, 38, 39], but the highest frequency relative to invasive ovarian cancer of these tumors occurs in the 15–29-year-old age group, and although symptomatic recurrence and death may rarely develop as late as 20 years after therapy, these neoplasms are correctly labeled as being of low malignant potential.

Treatment

Surgical excision of disease is the most effective therapy, and when necessary repeated explorations can be done, reserving chemotherapy for patients who develop ascites or whose tumor changes histologic features or demonstrates rapid growth. Disease extent at diagnosis, as well as histologic subtype, is an important prognostic factor [40, 41]. Fertility is an important consideration in planning treatment because patients often wish to attain a viable pregnancy. Most gynecologic oncologists recommend conservative therapy, especially in patients who are desirous of further childbearing and have stage IA disease [42]. While there is vast experience with fertility-sparing surgery with excellent oncologic outcomes, recent studies have been evaluating the best approach that optimizes the oncological and fertile balance [34]. Traditionally, fertility-sparing surgery had only been offered to patients with tumors limited to the ovary [42]. However, more recent reports suggest that fertility preservation may be safely offered to appropriately selected patients with advanced

disease [39, 43]. Most published series are heterogeneous with a preponderance of cases with early-stage disease, and data on the safety of ovarian conservation in advanced borderline tumors are lacking [29].

Even today BOT remain one of the most controversial topics, as the category has often led to both inadequate treatment and overtreatment. While fertility-sparing surgery is widely accepted and performed, there is a lack of randomized controlled trials evaluating its outcome, and consequently there is a lack of standardized treatment guidelines. Given BOT's general good prognosis, low mortality rates, and general short follow-up of most studies, the end point of these studies was recurrence-free survival, even though it is known that most BOT recurrences can be properly salvaged with surgical treatment. Most patients are cured after up-front surgery or even after salvage surgery for recurrent disease; however, a minority of patients recur as invasive disease (IOC), progress, and eventually succumb to the disease. Avoiding disease recurrence should be an important goal. The only known prognostic factors for progression to IOC remain residual disease after up-front surgery and the presence of invasive implants [26].

In summary, borderline tumors of the ovary carry a favorable prognosis, even when diagnosed at an advanced stage, with a high recurrence rate but limited mortality.

Fertility Preservation

Approximately 11% of invasive ovarian cancers are diagnosed in women aged 20–45 years, with more than half of these being early-stage cancers [5, 44]. According to the 2010 Surveillance Epidemiology and End Results (SEER) data, approximately 20,000 women less than 50 years old are diagnosed with gynecologic cancer each year. SEER statistics indicate approximately 47% of these women, or 10,000 total, will be present with localized disease [5, 45]. Young women with early-stage disease have an excellent prognosis [46] that is why issues affecting long-term survivors, including fertility preservation without compromising oncologic outcomes, have received growing attention. When the disease seems to be confined to one ovary, preservation of the uterus and contralateral ovary is increasingly being offered to women who wish to retain their childbearing ability [47].

Conservative treatment of epithelial ovarian cancer (EOC) is based on unilateral salpingo-oophorectomy and complete surgical staging. This is an option available to young women who present with an early-stage invasive tumor with a low risk of recurrence [46, 48, 49]. The outcomes for patients seem to be similar to those after conventional treatment of patients with stage IA (grades 1 and 2) and stage IC (grade 1) disease [46, 48, 49]. In the case of patients with stages IA and IC grade 3 diseases and stage IC grade 2 tumors, the results of conservative management continue to fuel debate [27, 48]. After conservative treatment for invasive ovarian cancer, term delivery rates have been reported as high as 30%, and successful pregnancy outcomes have been reported after adjuvant chemotherapy.

Conservative surgery is generally not recommended for patients with clear cell or carcinosarcoma or grade III tumors and when disease is present outside the ovaries. A careful discussion regarding the risks and benefits of this approach is essential. Maltaris and colleagues [50] reported that 12% of patients undergoing fertility-sparing ovarian cancer surgery experienced recurrence and 4% of patients died from their disease.

Previous studies on fertility-sparing laparoscopic surgery in the setting of an ovary-confined ovarian malignancy are based on single-institution experiences and owing to the low prevalence of young women diagnosed with invasive ovarian cancer; these studies have been limited by a small number of patients and inclusion of low malignant potential tumors. Although certainly limited by a small sample size, in some series, conservative surgical management with fertility preservation and conservation of an ovary after removing macroscopically apparent disease was not found to be associated with an increased risk of recurrence or with earlier recurrence. Counseling such patients can be difficult, as little is known about the chances of conceiving and/or the risks of cancer recurrence after fertility-sparing surgery (FSS) for gynecologic cancer [45].

This approach may be reasonably offered to young women who have not completed their childbearing.

The low recurrence rates and high overall survival observed for stage I ovarian cancers are of utmost importance when considering laparoscopic conservative treatment of early-stage disease in reproductive-aged women.

As more research is needed to determine whether the clearly defined benefits of minimally invasive surgery can be extrapolated to include patients undergoing fertility-sparing staging for early ovarian cancer without assuming unacceptable risk, Ghezzi et al. [47] decided to conduct a multi-institutional study including consecutive patients who underwent fertility-sparing laparoscopic treatment of early-stage ovarian carcinoma (EOC) at five Italian high-volume centers. Laparoscopic staging has been indicated as preferable, avoiding a midline laparotomy incision; this is particularly relevant in young women not only for the advantage of improved cosmetic but also because the open approach may result in more disruption of nerves as well as pelvic adhesions known to decrease fecundity [51]. Minimally invasive surgery may result in less tissue and organ handling and trauma, avoids contamination with foreign bodies, and facilitates more precise tissue manipulation, all of which may help to reduce risk for postoperative adhesion formation. Adhesions may affect fertility adversely by distorting adnexal anatomy and interfering with gamete and embryo transport [47].

Fertility-sparing surgery has been proposed as a safe alternative for selected young women with early-stage epithelial ovarian cancer who wish to preserve their fertility [52–56]. Retrospective studies suggest that fertility-sparing surgery can be performed safely for patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA and IC epithelial ovarian cancer, although there has not been a prospective trial [57].

Most studies have examined the safety of fertility-sparing surgery for serous adenocarcinoma of the ovary rather than clear cell carcinoma. Because clear cell

carcinoma is usually diagnosed as an early-stage disease among young women with endometriosis or during fertility treatment, the need for fertility-sparing surgery is very high [58, 59]. FSS has been found to be a safe and reasonable alternative for young women with FIGO stage IA and IC clear cell carcinoma of the ovary who wish to preserve their fertility. However, further evaluation is required to confirm this finding [2].

The management of pediatric and adolescent ovarian lesions must carefully balance maximal preservation of reproductive potential with adequate intervention to address the real risk of malignancy. However, preoperative malignancy status is typically unknown.

Rate of cystectomy (versus oophorectomy) varies widely with physician specialty, among other factors' [60] "correct" interventions:

1. Exploratory laparotomy with unilateral salpingo-oophorectomy and staging procedures per Children's Oncology Group (COG) guidelines [61]
2. Ipsilateral ovarian-sparing procedure with tumor enucleation/"cystectomy" (laparoscopic or open)
3. A combination of the two procedures

For children with ovarian tumors, the decision to pursue oncologic surgery, fertility-preserving surgery, or watchful waiting should be made after an individualized discussion involving the surgeon, patient, and family defined a risk stratification system for children with ovarian masses, based on preoperative laboratory values and tumor characteristics. For patients with heterogeneous ovarian tumors, tumor marker status is a useful decision point. Given the well-substantiated relationship between alpha fetoprotein and beta-hCG and malignancy, unilateral oophorectomy and surgical staging per COG guidelines are warranted [61].

The decision to undergo an ovarian-sparing or oncologic procedure should be individual, until further information becomes available. Furthermore, it is important to consider the option of a second-look procedure if surgical pathology was to unexpectedly return as positive for malignancy. Such a strategy may maximally preserve fertility for patients with moderate or indeterminate preoperative risk of malignancy. However, this benefit must be tempered by the potential missed opportunity for surveillance of stage I disease: among patients with positive margins after partial oophorectomy (who would otherwise have had stage I disease if an oncologic surgery had been performed), chemotherapy would be required after completion oophorectomy.

Patients with negative tumor markers:

- Those with non-large (≤9 cm) tumors

Malignancy rate was 2% and oophorectomy is unnecessary. Non-large solid tumors had an 11.1% malignancy rate. Negative tumor markers did not indicate a substantially lower malignancy rate (10.0%). Especially in such cases of non-large solid tumors, an informed discussion with the patient and her family is indispensable [62].

- Those with large (≥9 cm) tumors

31.3% of tumor marker-negative large heterogeneous tumors were malignant (most commonly immature teratomas). These lesions warrant caution and discussion of the risks and benefits of each surgical option. For individualized patients with negative tumor markers and large, heterogeneous tumors, ovarian-sparing surgery with a laparotomy and "controlled" cystectomy may be acceptable. For example, the presence of a "dermal plug" on ultrasound may potentially be reassuring for a benign process even in a large heterogeneous mass [63].

A policy of categorical oophorectomy with solid tumors, while not unreasonable, would miss the opportunity for fertility-preserving surgery among patients who have mature teratomas. These patients will face not only the burden of dealing with a cancer diagnosis but also the other attendant effects of early menopause [45].

References

1. Elsenhauer EL, Salani R, Copeland LJ. Epithelial ovarian cancer. Di Saia PJ. Clinical gynecologic oncology. 8th. Elsevier/Saunders. Philadelphia. 2012 285-328.
2. Park JY, Suh DS, Kim JH, Kim YM, Kim YT, Nam JH. Outcomes of fertility-sparing surgery among young women with FIGO stage I clear cell carcinoma of the ovary. Inter J Gynaecol Obstetrics Off Organ Inter Federation Gynaecol Obstetrics. 2016;134(1):49–52.
3. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet. 2014;384(9951):1376–88.
4. Kesic V. Fertility after the treatment of gynecologic tumors. Recent Results Cancer Res Fortschritte der Krebsforschung Progres dans les recherches sur le cancer. 2008;178:79–95.
5. A Snapshot of Ovarian Cancer. Incidence and Mortality. National Institute of Health: National Cancer Institute. 2014. Available from: http://www.cancer.gov/research/progress/snapshots/ovarian.
6. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9–29.
7. Trabert B, Lamb EJ, Scoccia B, Moghissi KS, Westhoff CL, Niwa S, et al. Ovulation-inducing drugs and ovarian cancer risk: results from an extended follow-up of a large United States infertility cohort. Fertil Steril. 2013;100(6):1660–6.
8. Brinton LA, Sahasrabuddhe VV, Scoccia B. Fertility drugs and the risk of breast and gynecologic cancers. Semin Reprod Med. 2012;30(2):131–45.
9. del Carmen MG, Birrer M, Schorge JO. Clear cell carcinoma of the ovary: a review of the literature. Gynecol Oncol. 2012;126(3):481–90.
10. Anglesio MS, Carey MS, Kobel M, Mackay H, Huntsman DG. Vancouver ovarian clear cell symposium S. Clear cell carcinoma of the ovary: a report from the first ovarian clear cell symposium, June 24th, 2010. Gynecol Oncol. 2011;121(2):407–15.
11. Heintz AP, Odicino F, Maisonneuve P, Beller U, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. Inter J Gynaecol Obstetrics Off Organ Inter Feder Gynaecol Obstetrics. 2003;83(Suppl 1):135–66.
12. Fathalla MF. Incessant ovulation – a factor in ovarian neoplasia? Lancet (London, England). 1971;2(7716):163.
13. Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, et al. Ovarian cancer risk after the use of ovulation-stimulating drugs. Obstet Gynecol. 2004;103(6):1194–203.
14. Silva Idos S, Wark PA, McCormack VA, Mayer D, Overton C, Little V, et al. Ovulation-stimulation drugs and cancer risks: a long-term follow-up of a British cohort. Br J Cancer. 2009;100(11):1824–31.

15. Sanner K, Conner P, Bergfeldt K, Dickman P, Sundfeldt K, Bergh T, et al. Ovarian epithelial neoplasia after hormonal infertility treatment: long-term follow-up of a historical cohort in Sweden. Fertil Steril. 2009;91(4):1152–8.
16. Lerner-Geva L, Rabinovici J, Olmer L, Blumstein T, Mashiach S, Lunenfeld B. Are infertility treatments a potential risk factor for cancer development? Perspective of 30 years of follow-up. Gynecol Endocrinol Off J Inter Soc Gynecol Endocrinol. 2012;28(10):809–14.
17. Mosgaard BJ, Lidegaard O, Kjaer SK, Schou G, Andersen AN. Infertility, fertility drugs, and invasive ovarian cancer: a case-control study. Fertil Steril. 1997;67(6):1005–12.
18. Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol. 2002;155(3):217–24.
19. Kurta ML, Moysich KB, Weissfeld JL, Youk AO, Bunker CH, Edwards RP, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. Cancer Epidemiol Biomarkers Prev Pub Am Asso Cancer Res Cosponsored Am Soc Preventive Oncol. 2012;21(8):1282–92.
20. McGuire V, Hartge P, Liao LM, Sinha R, Bernstein L, Canchola AJ, et al. Parity and oral contraceptive use in relation to ovarian cancer risk in older women. Cancer Epidemiol Biomarkers Prev Pub Am Asso Cancer Res Cosponsored Am Soc Preventive Oncol. 2016;25(7):1059–63.
21. Danforth KN, Tworoger SS, Hecht JL, Rosner BA, Colditz GA, Hankinson SE. Breastfeeding and risk of ovarian cancer in two prospective cohorts. Cancer Causes Control CCC. 2007;18(5):517–23.
22. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. IV. The pathogenesis of epithelial ovarian cancer. Collaborative Ovarian Cancer Group. Am J Epidemiol. 1992;136(10):1212–20.
23. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. N Engl J Med. 1994;331(12):771–6.
24. Modan B, Ron E, Lerner-Geva L, Blumstein T, Menczer J, Rabinovici J, et al. Cancer incidence in a cohort of infertile women. Am J Epidemio. 1998;147(11):1038–42.
25. Doyle P, Maconochie N, Beral V, Swerdlow AJ, Tan SL. Cancer incidence following treatment for infertility at a clinic in the UK. Hum Reprod. 2002;17(8):2209–13.
26. Jensen A, Sharif H, Frederiksen K, Kjaer SK. Use of fertility drugs and risk of ovarian cancer: Danish Population Based Cohort Study. BMJ. 2009;338:b249.
27. Bentivegna E, Fruscio R, Roussin S, Ceppi L, Satoh T, Kajiyama H, et al. Long-term follow-up of patients with an isolated ovarian recurrence after conservative treatment of epithelial ovarian cancer: review of the results of an international multicenter study comprising 545 patients. Fertil Steril. 2015;104(5):1319–24.
28. Mutch DG, Prat J. 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. Gynecol Oncol. 2014;133(3):401–4.
29. Helpman L, Beiner ME, Aviel-Ronen S, Perri T, Hogen L, Jakobson-Setton A, et al. Safety of ovarian conservation and fertility preservation in advanced borderline ovarian tumors. Fertil Steril. 2015;104(1):138–44.
30. Morris CR, Liu L, Rodriguez AO, Cress RD, Snipes K. Epidemiologic features of borderline ovarian tumors in California: a population-based study. Cancer Causes Control: CCC. 2013;24(4):665–74.
31. Kurman RJ, Trimble CL. The behavior of serous tumors of low malignant potential: are they ever malignant? Inter J Gynecol Pathol Off J Inter Society Gynecol Pathol. 1993;12(2):120–7.
32. Leake JF, Currie JL, Rosenshein NB, Woodruff JD. Long-term follow-up of serous ovarian tumors of low malignant potential. Gynecol Oncol. 1992;47(2):150–8.
33. Sherman ME, Mink PJ, Curtis R, Cote TR, Brooks S, Hartge P, et al. Survival among women with borderline ovarian tumors and ovarian carcinoma: a population-based analysis. Cancer. 2004;100(5):1045–52.

34. Vasconcelos I, de Sousa Mendes M. Conservative surgery in ovarian borderline tumours: a meta-analysis with emphasis on recurrence risk. Eur J Cancer. 2015;51(5):620–31.
35. Skirnisdottir I, Garmo H, Wilander E, Holmberg L. Borderline ovarian tumors in Sweden 1960-2005: trends in incidence and age at diagnosis compared to ovarian cancer. Int J Cancer. 2008;123(8):1897–901.
36. Wong HF, Low JJ, Chua Y, Busmanis I, Tay EH, Ho TH. Ovarian tumors of borderline malignancy: a review of 247 patients from 1991 to 2004. Inter J Gynecol Cancer Off J Inter Gynecol Cancer Soc. 2007;17(2):342–9.
37. Hannibal CG, Huusom LD, Kjaerbye-Thygesen A, Tabor A, Kjaer SK. Trends in incidence of borderline ovarian tumors in Denmark 1978-2006. Acta Obstet Gynecol Scand. 2011;90(4):305–12.
38. Prat J, De Nictolis M. Serous borderline tumors of the ovary: a long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion. Am J Surg Pathol. 2002;26(9):1111–28.
39. Zanetta G, Rota S, Chiari S, Bonazzi C, Bratina G, Mangioni C. Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective study. J Clin Oncol Off J Am Soc Clin Oncol. 2001;19(10):2658–64.
40. Ren J, Peng Z, Yang K. A clinicopathologic multivariate analysis affecting recurrence of borderline ovarian tumors. Gynecol Oncol. 2008;110(2):162–7.
41. Shih KK, Zhou Q, Huh J, Morgan JC, Iasonos A, Aghajanian C, et al. Risk factors for recurrence of ovarian borderline tumors. Gynecol Oncol. 2011;120(3):480–4.
42. Kaern J, Trope CG, Abeler VM. A retrospective study of 370 borderline tumors of the ovary treated at the Norwegian Radium Hospital from 1970 to 1982. A review of clinicopathologic features and treatment modalities. Cancer Causes Control CCC. 1993;71(5):1810–20.
43. Uzan C, Kane A, Rey A, Gouy S, Duvillard P, Morice P. Outcomes after conservative treatment of advanced-stage serous borderline tumors of the ovary. Ann Oncol Off J Eur Soc Med Oncol ESMO. 2010;21(1):55–60.
44. Ross L, Chung K, Macdonald H. Fertility preservation in the female cancer patient. J Surg Oncol. 2014;110(8):907–11.
45. Letourneau J, Chan J, Salem W, Chan SW, Shah M, Ebbel E, et al. Fertility sparing surgery for localized ovarian cancers maintains an ability to conceive, but is associated with diminished reproductive potential. J Surg Oncol. 2015;112(1):26–30.
46. Fotopoulou C, Braicu I, Sehouli J. Fertility-sparing surgery in early epithelial ovarian cancer: a viable option? Obstet Gynecol Int. 2012;2012:238061.
47. Ghezzi F, Cromi A, Fanfani F, Malzoni M, Ditto A, De Iaco P, et al. Laparoscopic fertility-sparing surgery for early ovarian epithelial cancer: a multi-institutional experience. Gynecol Oncol. 2016;141(3):461–5.
48. Morice P, Denschlag D, Rodolakis A, Reed N, Schneider A, Kesic V, et al. Recommendations of the fertility task force of the European society of gynecologic oncology about the conservative management of ovarian malignant tumors. Inter J Gynecol Cancer Off J Inter Gynecol Cancer Soc. 2011;21(5):951–63.
49. du Bois A, Heitz F, Harter P. Fertility-sparing surgery in ovarian cancer: a systematic review. Onkologie. 2013;36(7-8):436–43.
50. Maltaris T, Beckmann MW, Dittrich R. Review. Fertility preservation for young female cancer patients. In vivo (Athens, Greece). 2009;23(1):123–30.
51. Weber S, McCann CK, Boruta DM, Schorge JO, Growdon WB. Laparoscopic surgical staging of early ovarian cancer. Rev Obst Gynecol. 2011;4(3-4):117–22.
52. Satoh T, Hatae M, Watanabe Y, Yaegashi N, Ishiko O, Kodama S, et al. Outcomes of fertility-sparing surgery for stage I epithelial ovarian cancer: a proposal for patient selection. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(10):1727–32.
53. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, et al. Outcomes of fertility-sparing surgery for invasive epithelial ovarian cancer: oncologic safety and reproductive outcomes. Gynecol Oncol. 2008;110(3):345–53.

54. Fruscio R, Corso S, Ceppi L, Garavaglia D, Garbi A, Floriani I, et al. Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series. Ann Oncol Off J Eur Soc Med Oncol ESMO. 2013;24(1):138–44.
55. Ditto A, Martinelli F, Lorusso D, Haeusler E, Carcangiu M, Raspagliesi F. Fertility sparing surgery in early stage epithelial ovarian cancer. J Gynecol Oncol. 2014;25(4):320–7.
56. Kajiyama H. Fertility sparing surgery in patients with early stage epithelial ovarian cancer: implication of survival analysis and lymphadenectomy. J Gynecol Oncol. 2014;25(4):270–1.
57. Nam JH, Park JY. Fertility-sparing surgery for young women with early-stage epithelial ovarian cancer. Gynecol Obstet Investig. 2013;76(1):14–24.
58. Kajiyama H, Shibata K, Suzuki S, Ino K, Yamamoto E, Mizuno K, et al. Is there any possibility of fertility-sparing surgery in patients with clear-cell carcinoma of the ovary? Gynecol Oncol. 2008;111(3):523–6.
59. Kajiyama H, Shibata K, Mizuno M, Hosono S, Kawai M, Nagasaka T, et al. Fertility-sparing surgery in patients with clear-cell carcinoma of the ovary: is it possible? Hum Reprod. 2011;26(12):3297–302.
60. Berger-Chen S, Herzog TJ, Lewin SN, Burke WM, Neugut AI, Hershman DL, et al. Access to conservative surgical therapy for adolescents with benign ovarian masses. Obstet Gynecol. 2012;119(2 Pt 1):270–5.
61. Billmire D, Vinocur C, Rescorla F, Cushing B, London W, Schlatter M, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg. 2004;39(3):424–9.
62. Madenci AL, Levine BS, Laufer MR, Boyd TK, Voss SD, Zurakowski D, et al. Preoperative risk stratification of children with ovarian tumors. J Pediatr Surg. 2016;51(9):1507–12.
63. Ekici E, Soysal M, Kara S, Dogan M, Gokmen O. The efficiency of ultrasonography in the diagnosis of dermoid cysts. Zentralbl Gynakol. 1996;118(3):136–41.

Chapter 18
Endometrial Cancer

Definition

Endometrial cancer (EC) is defined by the ability of endometrial cancer cells to invade local tissue and metastasize; endometrial lesions are represented by glandular and stromal variations in continuous change [1]. In the setting of prolonged, unopposed estrogen exposure, the endometrium can become disordered, resulting in endometrial hyperplasia; this is a cancer precursor lesion that, if left untreated, has a high likelihood of progression to endometrial cancer [2].

Incidence

EC is the most common cancer of the female genital tract in most Western and high-income countries, with an incidence of 20 in 100,000 and is the fourth most common cancer in women of all ethnic origins, after breast, lung, and colorectal cancer [2, 3]. In the United States, cancer of the uterine corpus is the most common malignancy unique to women; recently deaths from uterine cancer have increased [1].

Epidemiology

Endometrial adenocarcinoma occurs during the reproductive and menopausal years and mainly affects postmenopausal women. The mean age for patients with adenocarcinoma of the uterine corpus is 63 years; most patients are between the ages of 50 and 59 years. Approximately 5% of women will have adenocarcinoma before the age of 40 years, and 20–25% will be diagnosed before menopause [1–4]; this means that a significant number of premenopausal nulliparous women will be diagnosed

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_18

with EC [3]. Incidence and survival are higher in white women compared with black women. There is a dramatic rise in the incidence rate of endometrial hyperplasia and endometrial cancer at 45 years of age and peaking at 65 years of age. This is a result of the combined effects of estrogen production in the peripheral adipose tissue, particularly in obese women, and the absence of progesterone that results from loss of ovulatory function in menopause [1].

Natural History

There are two pathogenic types of endometrial cancer.

Type 1 Endometrioid Adenocarcinoma

This is the most common of endometrial cancers (84%) associated with prolonged, unopposed estrogen exposure [2]. Patients with this pathogenic type mainly have well-differentiated or moderately differentiated tumor, superficial invasion of the myometrium, high sensitivity to progestins, and favorable prognosis (85% 5-year survival). Estrogen receptors are present in 90% of cases of endometrial cancer type I which usually develops from atypical endometrial hyperplasia [1].

Type 2

The second pathogenic type of disease arises in women who have none of these disease states or in whom the disease states are not clearly defined. The patients who fall into the second pathogenic group tend to have worse prognosis [1, 2, 5]. Endometrial cancers in women without evidence of excess estrogen are usually not associated with hyperplasia and can be associated with a tumor suppressor gene abnormality such as p53-associated uterine serous carcinomas; these are aggressive tumors, with higher mortality rates [1].

The endometrium is a very dynamic tissue in the reproductive-aged woman. It is continuously changing in response to hormonal, stromal, and vascular influences, with the intended goal of implanting an embryo and supporting the nutritional needs of the developing pregnancy [1]. Estrogen stimulation is associated with the growth and proliferation of the endometrium, whereas progesterone produced by the corpus luteum after ovulation inhibits proliferation and stimulates secretion in the glands and predecidual change in the stroma. Women have transitions in their lives—such as menopause or anovulation—during which the absence of ovulation predisposes them to unopposed estrogen stimulation because no corpus luteum forms to secrete progesterone. Continuous estrogen stimulation of the endometrium bypasses the normal recycling of the endometrium [1]. In the setting of prolonged and excessive exposure of the endometrium to estrogen without opposition by progesterone, the

endometrium can become disordered and will yield a continuous spectrum of change from proliferative endometrium through many variations of endometrial hyperplasia [1, 2]. Only those hyperplasias with cellular atypia are considered to be precursors of endometrial adenocarcinoma.

Etiology

Endocrine and paracrine contributions to endometrial pathology are well recognized.

For most patients with endometrioid-type tumors, particularly grade I–II lesions, and hyperplasia, hyperestrogenism is the etiologic basis. Until endometrial cancer screening becomes routine and cost-effective, the true prevalence of the precursor lesions will remain unknown [1] even though it has an estimated prevalence of 132 per 100,000 woman per year [6]. Up to 43% of patients with endometrial hyperplasia and cytologic atypia harbor a coexisting carcinoma [1].

The International Society of Gynecological Pathologists (ISGYP), the International Federation of Gynecology and Obstetrics (FIGO), and the World Health Organization (WHO) classify endometrial hyperplasia into four categories based on architectural structure and cytologic features. The architecture is either simple or complex, and the cytologic features are described as with or without atypia.

This yields four separate diagnoses:

- Simple hyperplasia without atypia
- Complex hyperplasia without atypia
- Simple hyperplasia with atypia
- Complex hyperplasia with atypia (AEH) [1]

The relationship of unopposed estrogen and endometrial cancer is well documented.

All causes of hyperestrogenic state are the main risk factors for developing endometrial hyperplasia and type I EC [2, 7].

- Age is the greatest independent risk factor associated with endometrial cancer or complex hyperplasia. The age at presentation depends on the source of the excess estrogen [1].
- Chronic anovulation (anovulatory cycles, prolonged perimenopause with anovulatory bleeding patterns).
- Obesity (excess body mass).
- Polycystic ovarian syndrome (prolonged anovulatory condition and hyperandrogenemia).
- Metabolic syndrome.
- Hyperinsulinemia and predisposition to type 2 diabetes mellitus, moreover, a role for insulin resistance and resulting downstream aberrations has been implicated in the pathogenesis of endometrial hyperplasia and endometrial cancer. Inflammation and insulin resistance are intimately related.
- Nulliparity.
- Late age at menopause.
- Menstrual irregularity.

- Hypertension.
- Administration of exogenous estrogen hormones alone carries an increased relative risk (RR) of endometrial cancer [8].
- Genetic syndromes: although most cases of endometrial cancer are sporadic, there are few recognized genetic syndromes associated with endometrial cancer. Reference to Chap. 2.

1. Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch II syndrome

This is an autosomal dominant-inherited cancer that involves a germline mutation; HNPCC is associated with a lifetime risk of 30–61% of developing endometrial cancer. There is also an increased risk of ovarian cancers and other nongynecologic cancers [1]. Lynch syndrome is the most common genetic mutation of relevance for endometrial cancer, resulting in a compound increased risk of colon cancer [9]. Premenopausal patients with endometrial cancer should also be counseled about the possibility of Lynch syndrome. A family history should be taken, and if endometrial and colon cancers are frequent in the family, the patient should be referred to genetic counseling [1].

2. Cowden syndrome

This is a rare condition resulting in mutation of the phosphatase and tensin homolog (PTEN) tumor suppressor gene that leads to a fivefold increased risk for endometrial cancer [9].

3. Mutations in the breast cancer 1 (BRCA1) gene

Also associated with endometrial cancer with a standard incidence ratio of 1.91 [10].

Clinical Manifestations

Endometrial hyperplasia is a lesion that is usually unrecognized and asymptomatic until cancer develops [1]. Women with endometrial hyperplasias are identified by endometrial biopsy performed because of abnormal vaginal bleeding (menorrhagia or postmenopausal bleeding) or because a thickened endometrial stripe is found on transvaginal ultrasound when ordered for another reason such as the identification of endometrial cells in the Pap test of a woman older than age 40 [1]. Irregular bleeding is a quite common early symptom, so most of these tumors (90%) are detected as well-differentiated (grade 1) endometrioid EC at a very early stage restricted to the endometrium or invading only superficially the myometrium [4, 11].

Diagnosis

Routine screening for uterine adenocarcinoma and its precursors is not recommended. All postmenopausal women with uterine bleeding must be evaluated for endometrial cancer, although only 20% of these patients will have a malignant

genital neoplasm [4]. As the patient's age increases after menopause, there is a progressively increasing probability that her uterine bleeding is caused by endometrial cancer. In the young patient, prolonged and heavy menstrual periods and intermenstrual spotting may indicate cancer, and endometrial sampling is advised. Most young patients who develop endometrial cancer are obese and often with anovulatory menstrual cycles.

Fractional Dilation and Curettage (D&C)

It has been the definitive diagnostic procedure used in ruling out endometrial cancer [1].

Endometrial Biopsy

Sampling the endometrium in symptomatic patients is the first diagnostic step. Today, most advocate the routine use of the endometrial biopsy as an office procedure to make a definitive diagnosis and spare the patient hospitalization and an anesthetic. The accuracy of the endometrial biopsy in detecting endometrial cancer is approximately 90%. If histologic findings are "negative," the patient is observed; D&C is done only if the patient continues to be symptomatic after the negative biopsy result [1]. Office endometrial biopsy has in general replaced the dilation and curettage procedure for the diagnosis of endometrial hyperplasia or carcinoma [1].

Hysteroscopy

Hysteroscopy is used frequently in the evaluation of patients with abnormal uterine bleeding and has the advantages of allowing the physician to see the pathologic lesion and direct biopsy, identify other competing diagnoses (fibroids, polyps), and perform the procedure on an outpatient basis. Hysteroscopy can also be used to evaluate the endocervical canal.

Tissue samples must be reviewed by an expert pathologist.

Ultrasonography (US)

Initial investigation with endometrial biopsy or US using a 4-mm cutoff was comparably cost-effective [1]. The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists issued an opinion on the role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding [12]. They

concluded that women with postmenopausal bleeding may be assessed initially with either endometrial biopsy or transvaginal ultrasonography. This initial evaluation does not require performance of both tests.

Pathology

Careful evaluation of the uterus by the pathologist is essential for proper diagnosis and treatment of corpus cancer. Gross inspection of the uterus at the time of hysterectomy can offer an impression of the size of the lesion, its location (involvement of the fundus, lower uterine segment, or cervix), and depth of tumor penetration into the myometrium (depth of invasion). Endometrial cancer may disseminate to regional lymph nodes, by embolization or direct extension into the pelvis or vagina or hematogenously to distant organs. The risk of spread is related to several factors, including depth of invasion into the myometrium, tumor grade, and histologic type [1].

Pathologically, endometrial cancer is characterized by the presence of glands in an abnormal relationship to each other, with little if any intervening stroma between the glands. Differentiation of adenocarcinoma is important prognostically and is the most important predictor of stage incorporated into FIGO surgical staging [1].

2009 FIGO Staging System for Carcinoma of the Endometrium

http://www.cancer.org/cancer/endometrialcancer/detailedguide/endometrial-uterine-cancer-staging

Endometrial Carcinoma Subtypes

Type	%
Endometrioid	84
Adenosquamous	4.2
Mucinous	0.9
Papillary serous	4.5
Clear cell	2.5
Squamous cell	0.04
Others	3.8

Serous adenocarcinoma (SC) (also called uterine papillary serous carcinoma, UPSC). This subtype represents less than 10% of all adenocarcinomas but is a

highly aggressive carcinoma of the uterus, not associated with hyperestrogenism, and frequently develops in the setting of atrophic endometrium. It is more commonly seen in older and nonwhite patients [1].

Tumor Grade

In addition to histologic type, pathologists assign a measure of tumor differentiation, known as grade. The degree of histologic differentiation of endometrial cancer is a sensitive indicator of prognosis and is included in FIGO stage assignment. Tumor grade is inversely related to survival decreases; as grade increases, survival is poorer. Both architectural criteria and nuclear grade are used to classify. Architectural grade is related to the proportion of solid tumor growth.

Determination of tumor pathological type and grade is done via dilatation and curettage of the uterine cavity or hysteroscopy.

Prognostic Factors

- Histologic type (pathology)
- Histologic differentiation
- Stage of disease (size and extent of tumor, depth of invasion, cervical involvement, adnexal involvement, and nodal metastasis)
- Myometrial invasion
- Peritoneal cytology
- Lymph node metastasis
- Adnexal metastasis

Prevention of Endometrial Cancer

Identification of at-risk individuals

Lifestyle Modifications

In 2007, the World Cancer Research highlighted the importance of healthy living for the prevention of endometrial cancer (www.aicr.org). Weight gain during adulthood, especially in the perimenopausal period, increases the risk of endometrial cancer irrespective of the BMI [13]. Counseling at-risk patients and encouraging

diet, exercise, and lifestyle modifications could potentially attenuate the risk of endometrial pathology in addition to the other obesity-related comorbidities [2].

Periodic Exposure to Progestins

The addition of a progestin appears to be protective [1]. *Periodic exposure to progestins* is a safe and efficacious preventive strategy against endometrial hyperplasia and endometrial cancer. Endometrial stimulation by estrogens unopposed by progestins leads to endometrial hyperplastic conditions in a dose- and time-dependent manner. The official position statement of the North American Menopause Society is that a progestogen should be added to estrogen therapy for all postmenopausal women with an intact uterus. The type, route, or regimen can be individualized to minimize side effects while providing adequate endometrial protection [1]. Women with a BMI of more than 22 could particularly benefit from high-potency progestin therapy [10]. The levonorgestrel IUD delivers a potent progestin directly to the endometrial cavity and confers a substantially decreased risk of endometrial hyperplasia, even among high-risk patients such as those undergoing treatment for breast cancer with tamoxifen or receiving estrogen therapy [14]. The premenopausal use of depot medroxyprogesterone acetate is associated with an 80% reduction of the risk of endometrial cancer [15].

Oral Contraceptives

Data indicate that the use of combination oral contraceptives decreases the risk for development of endometrial cancer. The use of combined oral contraceptives has shown a significantly reduced relative risk for endometrial cancer with every 5 years of use [16].

Women at very high risk for endometrial cancer, including those with genetic mutations predisposing to hereditary cancer, should consider beginning annual screening at the age of 35 years with annual transvaginal ultrasonography assessment and biopsy if appropriate [17]. Preventative hysterectomy should be discussed on a case-by-case basis. Having a first-degree family member with endometrial cancer increases a woman's risk [9].

Treatment

Management of Atypical Endometrial Hyperplasia (AEH)

Management decisions in women with AEH are complex and require an understanding of the risk of invasive endometrial adenocarcinoma, the reproductive desires of the patient, her comorbidities, and risks for surgical management.

Ideal and standard treatment of AEH is total hysterectomy via laparoscopic-assisted vaginal hysterectomy with or without bilateral salpingo-oophorectomy depending on the age of the patient. The finding of adenocarcinoma in the uterus requires determining whether observation or reoperation for surgical staging should be considered.

The patient's age, fertility plans, and need for contraception, comorbidities, and personal preferences play a key role in the management of these lesions. Hysterectomy is indicated when fertility is not desired and AEH is identified. AEH is commonly found with coexisting undiagnosed cancer already present in the uterus or progressing to endometrial cancer in untreated women [1]. The recommendation is that the patient should be informed of the risk of underlying malignancy. She should be counseled about the desire to keep her ovaries or have them removed, based on her age, family history, and other medical conditions or comorbidities. In the event that high-grade cancer or deep myometrial invasion is found, another surgery may be necessary for comprehensive surgical staging and removal of retained ovaries. Staging can usually be accomplished laparoscopically if a previous laparotomy was not performed [1].

Women who desire childbearing, refuse hysterectomy, or have medical conditions that make hysterectomy an undesirable first choice can be treated hormonally. The ACOG Practice Bulletin on endometrial cancer includes this general guideline: women with AEH and endometrial cancer who desire to maintain their fertility may be treated with progestin therapy. After therapy they should undergo serial complete intrauterine evaluation approximately every 3 months to document response. Hysterectomy should be recommended for women who do not desire fertility. Local therapy of the endometrium with a progestin-containing IUD is encouraging [18].

Management of Hyperplasia Without Atypia

The diagnosis of simple or complex hyperplasia without atypia requires hormonal management and is not an indication for hysterectomy. These lesions are generally reversible with progestogen (synthetic progestin or progesterone) [1].

Management of Endometrial Cancer

Surgical Treatment

Once a diagnosis of endometrial cancer is established, the patient should be assessed for surgical options of therapy. Hysterectomy remains the gold-standard definitive management strategy for these pathologies [3]. Most patients with endometrial cancer are candidates for definitive surgery, including surgical staging (lymphadenectomy). Routes of hysterectomy include vaginal, abdominal, laparoscopic (total or assisted), and robotic and have broadened the surgical options for patients.

Standard treatment in early-stage EC is total hysterectomy with or without salpingo-oophorectomy. Removal of the uterus removes the primary tumor and can provide important information that can be used to estimate risk of spread to the lymph nodes or risk of recurrence. Removal of the adnexa is thought to be important given that approximately 5% of endometrial cancers have metastatic disease to the ovaries and/or fallopian tubes. In addition, synchronous ovarian and endometrial cancers are not infrequent, particularly in younger patients [1].

Surgical evaluation of most patients with endometrial cancer requires total hysterectomy and bilateral salpingo-oophorectomy with inspection of the peritoneal cavity and collection of cytologic peritoneal washings, with or without pelvic and para-aortic lymphadenectomy [19]. Patients with negative lymph nodes are at very low risk of recurrence.

Chemotherapy

Chemotherapy has become increasingly used in the first-line management of advanced-stage and high-risk early-stage patients. Although the overall prognosis of patients in adjuvant radiation trials has been favorable, 3–23% of patients have a recurrence at distant sites, demonstrating the need for effective systemic therapy [1].

Radiation Therapy

Radiation therapy has been the adjuvant of choice for patients at risk of recurrence. Following radiation (vaginal or pelvic), vaginal cuff recurrences are uncommon.

Follow-Up

The aim of surveillance after treatment of endometrial cancer is the detection of treatable recurrent disease. Following surgery, with or without adjuvant therapy, patients with endometrial cancer should enter a routine surveillance program; they need to be seen every 3–4 months for the first 2 years, then yearly. Most recurrences are manifested within 2 years, making closer surveillance during this time reasonable. Surveillance visits should include a focused review of systems (questions related to pelvic, leg, or back pain; vaginal bleeding; urinary changes; changes in bowel habits) and physical examination including pelvic examination. It is important to perform Pap smears as a sampling of the vaginal cuff for early detection of vaginal cuff recurrences. Some have suggested that routine Pap smears are not cost-effective and that most recurrences are clinically palpable or associated with patient

symptoms. Radiation may produce cytologic changes occasionally difficult to classify [20].

Monitoring with CA 125 is helpful, primarily in patients with high risk for recurrent disease, as in patients with recurrent disease receiving therapy who have a proven elevation of their serum value.

Even though most of the patients with endometrial carcinoma do not experience recurrence or die because of this disease, the number of endometrial cancer deaths has risen over the past several years. Patients with recurrence at a distant site or with multiple sites of recurrence are best treated with hormonal or chemotherapy [1].

Effect on Fertility

Although gynecological cancers generally affect older women, a significant number of affected women are of childbearing age. These cancers may be part of the polycystic ovarian syndrome or the anovulatory transition before menopause and are all theoretically preventable with proper counseling and active management. Also the trend toward late childbearing has made fertility preservation a major issue in the treatment of young women with gynecological cancer [21]. More and more women in the near future, experiencing EC, will be asking for fertility-sparing options. The gynecological oncology society needs to reach a consensus on how to manage these women conservatively without compromising their survival outcome.

Fertility Preservation

Improved oncological outcomes have meant that increased attention is now being paid to quality of life issues, such as the childbearing potential for young women. The surgical treatment of cervical, endometrial, and ovarian cancers has traditionally involved the removal of the uterus, fallopian tubes, and/or ovaries, regardless of the patient's desires and of the impact on fertility [22]. However, fertility-sparing procedures can now be offered to young women affected by gynecological malignancies at an early stage. Fertility-sparing treatments have been successfully employed in selected endometrial cancer cases, and gynecologists should be familiar with fertility-preserving options for women with gynecological malignancies [23].

Young women with endometrial carcinoma generally have a more favorable prognosis at the moment of diagnosis due to the early stage and good differentiation [24]. Avoiding undertreatment and cancer recurrence requires appropriate patient selection for fertility-sparing endometrial cancer treatment [1].

The most important issues a treating physician has to consider before offering a conservative approach to women with EC are mainly divided in two categories:

- Tumor histological type, grade, myometrial invasion, and presence of lymphovascular space invasion
- Choosing the optimal type, dose, and duration of medical treatment, as well as the proper follow-up

In endometrial cancer cases, fertility sparing can be considered only in early-stage disease (stage IA grade 1) with well-differentiated adenocarcinoma and with no myometrial invasion and extrauterine spread upon pelvic imaging [25]. The Society for Gynecologic Oncology [19] mandates that imaging be performed to exclude a concurrent carcinoma before expectant management of a patient with atypical hyperplasia; MRI seems the most accurate imaging technique to detect myometrial involvement. Vaginal sonographic scans are also accurate (near 90%) [26]. Colonoscopy is often recommended to patients with endometrial cancer because of the association with colon cancer.

The mortality associated with conservative treatment of EC is extremely low despite the fact that the rate of recurrence is very high. This is attributed to the fact that in this setting, most of recurrences were salvageable with hysterectomy only [4].

Fertility preservation options in endometrial cancer:

- Hormonal treatment
- Fertility-sparing surgical procedures
- Both

The use of progestins seems to offer very good results in treating early-stage EC and allowing young women to pursue a pregnancy. Hormonal treatment with progesterone may be an option also for women who cannot have surgery because of other medical reasons [3].

This option usually is only recommended for women who:

- Have slower-growing cancer that has not reached the muscle layer of the uterus
- Do not have cancer outside of the uterus
- Are in general have good health and are able to take progestin
- Understand that information about future outcomes is limited

The premise for progesterone treatment is the concept that unopposed estrogen stimulation is the driver for both initiation and progression of EC [3] .

Endometrial tumors usually express hormone receptors and are sensitive to progesterone therapy. In patients who desire fertility preservation with detailed counseling, conservative management with high-dose progestin treatment may be considered to allow a disease-free window in which to attempt pregnancy [27, 28]. The most extended schema involves a high-dose progestin treatment [29] or a levonorgestrel intrauterine device (IUD) after hysteroscopic tumor resection [30, 31]. The progesterone-releasing IUD is a system to treat estrogen-dependent endometrial cancer; it provides very high doses of the hormone at the specific pathology site, which avoids the adverse effects produced by systemic administration. The initial response rate to hormonal treatment is generally good. However, there is a

high risk of relapse. Women who opt for hormonal treatment should clearly be informed about the risks and benefits of progestin treatment including the lack of response or disease progression while on hormonal therapy. Patients should be encouraged to pursue pregnancy very soon after complete remission of their disease has been confirmed histologically [5, 29].

Hysteroscopic control with endometrial biopsy must be conducted every 3–6 months until pregnancy [32]. Maintenance treatment is advisable if immediate pregnancy is not pursued. During pregnancy, it is difficult to safely sample the endometrium; after delivery, curettage should be performed to rule out a concurrent malignancy [6].

Conservative gynecological surgery is defined as surgery with preservation of at least the uterine corpus and part of one ovary. New surgical options enable young patients to achieve pregnancy after cancer treatment, although most will require the use of assisted reproductive techniques (ART) [21].

Research in EC cell lines has very recently yielded very interesting results regarding the use of the antidiabetic drug metformin and its effect on EC cells. These studies have shown that metformin suppresses EC cell growth and exhibits an antiproliferative effect in women with EC and insulin resistance. These preliminary reports may shift the future of conservative management of EC and provide more targeted ways of treatment, especially for patients with PCOS and insulin resistance [33].

Young women with EC should always be carefully consulted about the need for a genetic test for detection of Lynch syndrome. This will alert and identify patients with Lynch syndrome who need a very close monitoring and tailored consultation about their further follow-up and management [4]. It is debatable whether a patient with Lynch syndrome should be offered conservative management, and this becomes even more complicated in cases where hyperestrogenic state is also identified as a possible cause of an early EC. The detailed information about all aspects and risks of conservative treatment has to be provided and informed consent obtained, before initiation of the treatment. Basic rule of individualization of care as each patient has different characteristics as well as different needs and expectations [4].

For younger patients, with reassuring ovarian reserve without anovulation or severe male factor, spontaneous conception may be attempted for a limited time period. However, spontaneous conception may take several months, especially for premenopausal endometrial cancer patients affected by conditions that predispose to subfertility; this can lead to anxiety about the risk of recurrent disease during the preconception period and the delay of complementary surgery following childbearing [34]. Patients with previous history of infertility or with risk factors for infertility (obesity, PCOS, diabetes, anovulatory syndrome) should be referred to fertility specialist and probably will need assisted reproductive techniques to achieve pregnancy earlier, minimizing the risk of recurrence. Efficient ART therapies have helped successful pregnancies to be increasingly reported [34–40]. The use of assisted reproductive technologies such as in vitro fertilization (IVF) resulted in a 39.4% live birth rate compared with 14.9% in patients who conceived spontaneously [41]. There is insufficient literature to guide the timing of fertility treatment

initiation after the attainment of histological regression. During ovarian stimulation with high-dose gonadotrophin, the impact of a high serum estradiol concentration on endometrial carcinoma is unclear, although some data suggest the disadvantage of ovarian stimulation. Apparently, there is no clear optimal duration, protocol, or number of attempts for ovarian stimulation in patients with early-stage endometrial carcinoma. While ART use does not appear to increase endometrial cancer recurrence, available data must be interpreted cautiously as very few cases have been reported. In early trials of cases with existing endometrial cancer, the endometrium has usually been regularized with high-dose progestin treatment before attempting IVF with conventional stimulation protocols. Tests in endometrial cancer show that the use of letrozole with gonadotrophins can provide further protection [42].

During pregnancy, it is difficult to safely sample the endometrium; after delivery, curettage should be performed to rule out a concurrent malignancy [6]. The fertility outcomes in patients with endometrial pathology managed conservatively are reassuring, but women must be informed that hysterectomy remains the standard care option for atypical endometrial hyperplasia and endometrial cancer. After the completion of childbearing, some practitioners routinely recommend definitive hysterectomy with or without ovarian preservation [43] and, if indicated, surgical staging [19]. The routine employment of hysterectomy and oophorectomy is controversial, and therapy should be individualized. Patients with high and persistent endogenous estrogen levels may be encouraged to undergo hysterectomy due to the high risk of recurrence.

New developments in assisted reproductive technologies, including cryopreservation of ovarian tissue, oocytes, or embryos, have extended available options to young gynecological cancer patients [44]. Such cases should be managed in a reference center, which can coordinate surgical management, follow-up, and gestation management.

References

1. Landrum LMZ, Walker JL. Endometrial hyperplasia, estrogen therapy, and the prevention of endometrial cancer. In: Di Saia JDC, Creasman WT, editors. Clinical gynecologic oncology. 18th ed. St. Louis: Elsevier; 2012. p. 121–39.
2. Gressel GM, Parkash V, Pal L. Management options and fertility-preserving therapy for premenopausal endometrial hyperplasia and early-stage endometrial cancer. Int J Gynaecol Obstet: Off Organ Int Federat Gynaecol Obstet. 2015;131(3):234–9.
3. van Gent MD, Nicolae-Cristea AR, de Kroon CD, Osse EM, Kagie MJ, Trimbos JB, et al. Exploring morphologic and molecular aspects of endometrial cancer under progesterone treatment in the context of fertility preservation. Int J Gynecol Cancer: Off J Int Gynecol Cancer Soc. 2016;26(3):483–90.
4. Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V, et al. European society of gynecological oncology task force for fertility preservation: clinical recommendations for fertility-sparing management in young endometrial cancer patients. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2015;25(7):1258–65.

5. Baker J, Obermair A, Gebski V, Janda M. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. Gynecol Oncol. 2012;125(1):263–70.
6. Kalogiannidis I, Agorastos T. Conservative management of young patients with endometrial highly-differentiated adenocarcinoma. J Obstet Gynaecol: J Instit Obstet Gynaecol. 2011;31(1):13–7.
7. Hale GE, Hughes CL, Cline JM. Endometrial cancer: hormonal factors, the perimenopausal "window of risk," and isoflavones. J Clin Endocrinol Metab. 2002;87(1):3–15.
8. Chlebowski RT, Anderson GL. Menopausal hormone therapy and cancer: changing clinical observations of target site specificity. Steroids. 2014;90:53–9.
9. Shai A, Segev Y, Narod SA. Genetics of endometrial cancer. Familial Cancer. 2014;13(3):499–505.
10. Maxwell GL, Schildkraut JM, Calingaert B, Risinger JI, Dainty L, Marchbanks PA, et al. Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. Gynecol Oncol. 2006;103(2):535–40.
11. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecol Oncol Group Study Cancer. 1987;60(8 Suppl):2035–41.
12. ACOG Committee Opinion No 440. The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. Obstet Gynecol. 2009;114(2 Pt 1):409–11.
13. Xu WH, Xiang YB, Zheng W, Zhang X, Ruan ZX, Cheng JR, et al. Weight history and risk of endometrial cancer among Chinese women. Int J Epidemiol. 2006;35(1):159–66.
14. Ewies AA, Alfhaily F. Use of levonorgestrel-releasing intrauterine system in the prevention and treatment of endometrial hyperplasia. Obstet Gynecol Surv. 2012;67(11):726–33.
15. Kaunitz AM. Depot medroxyprogesterone acetate contraception and the risk of breast and gynecologic cancer. J Reprod Med. 1996;41(5 Suppl):419–27.
16. Collaborative Group on Epidemiological Studies on Endometrial Cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 2015;16(9):1061–70.
17. Smith RA, Brooks D, Cokkinides V, Saslow D, Brawley OW. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. CA Cancer J Clin. 2013;63(2):88–105.
18. Practice Bulletin No 149. Endometrial cancer. Obstet Gynecol. 2015;125(4):1006–26.
19. Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, et al. Management of endometrial precancers. Obstet Gynecol. 2012;120(5):1160–75.
20. Salani R, Backes FJ, Fung MF, Holschneider CH, Parker LP, Bristow RE, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: society of gynecologic oncologists recommendations. Am J Obstet Gynecol. 2011;204(6):466–78.
21. Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin. 2013;63(1):11–30.
22. Vitobello D, Siesto G, Bulletti C, Accardi A, Levi Setti PE. Gynecological fertility-sparing surgery. Placenta. 2011;32(Suppl 3):S224–31.
23. Martinez M, Rabadan S, Domingo J, Cobo A, Pellicer A, Garcia-Velasco JA. Obstetric outcome after oocyte vitrification and warming for fertility preservation in women with cancer. Reprod BioMed Online. 2014;29(6):722–8.
24. Rackow BW, Arici A. Endometrial cancer and fertility. Curr Opin Obstet Gynecol. 2006;18(3):245–52.
25. Yarali H. A successful pregnancy after intracytoplasmic sperm injection and embryo transfer in a patient with endometrial cancer who was treated conservatively. Fertil Steril. 2004;81(1):214–6.
26. Jantarasaengaram S, Praditphol N, Tansathit T, Vipupinyo C, Vairojanavong K. Three-dimensional ultrasound with volume contrast imaging for preoperative assessment of myome-

trial invasion and cervical involvement in women with endometrial cancer. Ultrasound Obstet Gynecol: Off J Int Soc Ultrasound Obstet Gynecol. 2014;43(5):569–74.
27. Eftekhar Z, Izadi-Mood N, Yarandi F, Shojaei H, Rezaei Z, Mohagheghi S. Efficacy of megestrol acetate (megace) in the treatment of patients with early endometrial adenocarcinoma: our experiences with 21 patients. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2009;19(2):249–52.
28. Hahn HS, Yoon SG, Hong JS, Hong SR, Park SJ, Lim JY, et al. Conservative treatment with progestin and pregnancy outcomes in endometrial cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2009;19(6):1068–73.
29. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95(1):133–8.
30. Chiva L, Lapuente F, Gonzalez-Cortijo L, Carballo N, Garcia JF, Rojo A, et al. Sparing fertility in young patients with endometrial cancer. Gynecol Oncol. 2008;111(2 Suppl):S101–4.
31. Mazzon I, Corrado G, Masciullo V, Morricone D, Ferrandina G, Scambia G. Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. Fertil Steril. 2010;93(4):1286–9.
32. Gadducci A, Spirito N, Baroni E, Tana R, Genazzani AR. The fertility-sparing treatment in patients with endometrial atypical hyperplasia and early endometrial cancer: a debated therapeutic option. Gynecol Endocrinol: Off J Int Soc Gynecol Endocrinol. 2009;25(10):683–91.
33. Soliman PT, Zhang Q, Broaddus RR, Westin SN, Iglesias D, Munsell MF, et al. Prospective evaluation of the molecular effects of metformin on the endometrium in women with newly diagnosed endometrial cancer: A window of opportunity study. Gynecol Oncol. 2016;143(3):466–71.
34. Gurgan T, Bozdag G, Demirol A, Ayhan A. Preserving fertility before assisted reproduction in women with endometrial carcinoma: case report and literature review. Reprod BioMed Online. 2007;15(5):561–5.
35. Lowe MP, Cooper BC, Sood AK, Davis WA, Syrop CH, Sorosky JI. Implementation of assisted reproductive technologies following conservative management of FIGO grade I endometrial adenocarcinoma and/or complex hyperplasia with atypia. Gynecol Oncol. 2003;91(3):569–72.
36. Demirol A, Bahce M, Ayhan A, Gurgan T. Pregnancy following intracytoplasmic sperm injection and preimplantation genetic diagnosis after the conservative management of endometrial cancer. Reprod BioMed Online. 2005;10(6):770–3.
37. Elizur SE, Beiner ME, Korach J, Weiser A, Ben-Baruch G, Dor J. Outcome of in vitro fertilization treatment in infertile women conservatively treated for endometrial adenocarcinoma. Fertil Steril. 2007;88(6):1562–7.
38. Bozdag G, Yarali H, Polat M, Esinler I, Tiras B, Ayhan A. ICSI outcome following conservative fertility sparing management of endometrial cancer. Reprod BioMed Online. 2009;18(3):416–20.
39. Sodano M, Bogliatto F, Morero S, Mosso L, Torchio B, Leidi L. Case report: Successful IVF programme after conservatively treated endometrial cancer. Reprod BioMed Online. 2009;18(4):578–81.
40. Chao AS, Chao A, Wang CJ, Lai CH, Wang HS. Obstetric outcomes of pregnancy after conservative treatment of endometrial cancer: case series and literature review. Taiwanese J Obstet Gynecol. 2011;50(1):62–6.
41. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2012;207(4):266. e1–12
42. Azim A, Oktay K. Letrozole for ovulation induction and fertility preservation by embryo cryopreservation in young women with endometrial carcinoma. Fertil Steril. 2007;88(3):657–64.

43. Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. BJOG: Int J Obstet Gynaecol. 2005;112(3):317–20.
44. Leblanc E, Narducci F, Ferron G, Querleu D. Indications and teaching of fertility preservation in the surgical management of gynecologic malignancies: European perspective. Gynecol Oncol. 2009;114(2 Suppl):S32–6.

Chapter 19
Cervical Cancer

Epidemiology

Cervical cancer is on a worldwide basis the most common gynecological malignancy [1]. Its incidence and mortality rates have declined more than 45% in the United States in the last two decades, but the disease remains a serious health threat. Despite recent declines, mortality rates in African American women remain higher than women of any other racial/ethnic group in the United States [2]. Also incidence rates in Hispanic women and American Indian/Alaska Native women are higher. Cervical cancer mortality and incidence rates vary with socioeconomic status and geographic location, and cervical cancer screening rates vary across racial/ethnic, socioeconomic, and geographic groups [2]. Ethnic and racial disparities still exist [3] probably as a result of a historical absence of effective screening programs [4].

Natural History

Approximately 35 human papillomavirus (HPV) subtypes infect the genital tract. Sexually transmitted, high-risk types of HPV (HPV 16 and HPV 18) are said to be present in about 70% of all squamous cervical cancers and 80% of all adenocarcinomas; type 18 is more frequently associated with adenocarcinoma of the cervix and type 16 with squamous cancer [3]. HPV causes a disease that will develop in the transformation zone. The transformation zone is that area on the cervix that undergoes squamous metaplasia, which develops mainly during the adolescent years.

About 20 million Americans and 630 million people worldwide are infected with HPV. In the United States, about 6.2 million will acquire a new infection every year. Infection with high-risk HPV is necessary or required but is not a sufficient factor for the development of squamous cervical neoplasia and nearly all types of cervical cancer. Only a small fraction of women infected with HPV will develop high-grade

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3_19

cervical abnormalities and cancer [3]. The current model of cervical carcinogenesis suggests that HPV infection results in either transient or persistent infection. Fortunately, for most women, particularly those who are young, their immune system is effective and clears the infection. In most cases, they are cleared within 1–2 years without producing neoplastic changes. The risk of neoplasia increases in those women in whom the infection persists. There does appear to be a high prevalence of the infection in teenagers, peaking in the 30s with subsequent decrease. Most lesions present in teenagers spontaneously regress [3].

Most HPV infection is transient and possesses little risk of progression. Few infections persist, but persistence at 1 year and 2 years [3] strongly predicts subsequent risk of high-grade cervical intraepithelial neoplasia 3 (CIN 3) regardless of age. These persistent infections, manifested by CIN 2 histology, are true cancer precursors.

Risk factors known to increase the likelihood of persistence include:

- Cigarette smoking.
- Compromised immune system.
- *Human immunodeficiency virus* (HIV) infection.
- HPV infection is most common in teenagers and women in their early 20s. Although prevalence decreases as women age, the lifetime cumulative risk is at least 80%. Most young women, especially those younger than 21 years, have an effective immune response that clears the infection in an average of 8 months or reduces the viral load in 85–90% of women to undetectable levels in an average of 8–24 months.

Cervical Intraepithelial Neoplasia (CIN)

CIN 1 is a manifestation of acute HPV infection and has a high rate of regression to normal cells. These lesions usually can be managed expectantly.

CIN 2 seems to represent a mix of low-grade and high-grade lesions not easily differentiated by routine histology rather than a specific intermediate-grade lesion.

CIN 3 and adenocarcinoma in situ (AIS) are clearly cancer precursors. Progression from persistent infection to cancer is slow, and the time course from CIN 3 to invasive cancer averages between 8.1 years and 12.6 years [3].

Histologic Classification of Cervical Cancer

Epithelial Tumors

Nonglandular:

- *Squamous cell carcinoma*: approximately 75–80% of cervical cancers are squamous cell, and most of the remaining cases are adenocarcinomas.
- Verrucous carcinoma.

- Warty (condylomatous) carcinoma.
- Papillary squamotransitional carcinoma.
- Lymphoepithelial-like carcinoma.
- Sarcomatoid carcinoma.

Glandular:

- *Adenocarcinoma*, usual endocervical type
- Mucinous adenocarcinoma
- Endometrioid adenocarcinoma
- Well-differentiated villoglandular adenocarcinoma
- Adenoma malignum (minimal deviation)
- Intestinal-like adenocarcinoma
- Signet ring cell adenocarcinoma
- Colloid adenocarcinoma
- Clear cell adenocarcinoma
- Serous papillary adenocarcinoma
- Mesonephric adenocarcinoma

Others, including mixed:

- Adenosquamous
- Glassy cell carcinoma
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Adenoid basal carcinoma
- Small cell carcinoma
- Classical carcinoid tumor
- Gestational choriocarcinoma

Nonepithelial Tumors

- Mesenchymal tumors
- Germ cell tumors
- Miscellaneous

Risk Factors

- Oncogenic subtypes of HPV have been identified as the etiologic cause of cervical neoplasia. The power, consistency, and specificity of the association between subclinical HPV infection and cervical neoplasia raise the strong possibility that *this relationship is causal* [3].
- Multiparity.

- Age: 45 and 55 years who married and delivered her first child at a young age.
- Starting sexual intercourse at an early age.
- Having first child at early age [3].
- Smoking.
- HIV or other immunodepression.
- Prior abnormal Pap test, previous dysplasia, and treatment.

Clinical Manifestations

- Early phases may be *asymptomatic*; they can be detected by currently available methods [5].
- Intermittent, painless *metrorrhagia* or spotting only postcoitally or after douching, although it is not the most common symptom (abnormal vaginal bleeding or discharge). As the malignancy enlarges, the bleeding episodes become heavier and more frequent, and they last longer. The patient may also describe what seems to her to be an increase in the amount and duration of her regular menstrual flow; the bleeding may become continuous. In the postmenopausal woman, the bleeding is more likely to prompt early medical attention [3].
- *Pain* during intercourse.

Symptoms or indicators of more advanced disease include:

- Development of pain referred to the flank, or leg, which is usually secondary to the involvement of the ureters, pelvic wall, or sciatic nerve routes.
- Dysuria, hematuria, rectal bleeding, or obstipation: resulting from bladder or rectal invasion. Distant metastasis and persistent edema of one or both lower extremities as a result of lymphatic and venous blockage by extensive pelvic wall disease are late manifestations of primary disease and frequent manifestations of recurrent disease. Massive hemorrhage and development of uremia with profound inanition may also occur and occasionally be the initial presenting symptom [3].
- Pelvic pain.
- Sciatica.
- Weight loss.
- Bone pain.

Diagnosis

For early stages or premalignant disease:

- Papanicolau, screening test.
- Human papillomavirus testing*:* testing high-risk (oncogenic) HPV only [3].
- Colposcopy with directed biopsy remains the standard for disease detection and is the technique of choice for treatment decisions [3].

- Cervical biopsy: for histologic diagnosis.
- Endocervical curettage or sampling may be conducted either by traditional ECC with a sharp curette, with vigorous endocervical brushing, or both [3].
- Cervical conization if CIN 2 or CIN 3 or carcinoma in situ (CIS).

Macroscopic lesions (invasive cancer):

- Clinical diagnosis

Three categories of gross clinical lesions:

1. Exophytic lesion
2. Infiltrating tumor that tends to show little visible ulceration or exophytic mass but is initially seen as a stone-hard cervix
3. Ulcerative tumor

  - Pelvic examination under anesthesia: evaluation of tumor size and involvement of vagina, rectum, and parametria.
  - Clinical staging is enhanced with the liberal use of rectovaginal examinations in that this type of pelvic examination allows more complete palpation of the parametria and cul-de-sac [3].

- Pathology and Imaging

  - Cervical biopsy for histologic diagnosis.
  - Image studies to evaluate tumor size and other organs compromise (does not change staging): PET-CT showed the highest pooled sensitivity (82%) and specificity (95%).
  - RNM.
  - CT.

Findings of PET-CT or conventional MR and/or CT examinations can be used in the planning of therapy but should not influence the initial clinical staging of the lesion.

Staging

The staging of cancer of the cervix is a clinical, preferably confirmed with the patient under anesthesia; it cannot be changed later if findings at operation or subsequent treatment reveal further advancement of the disease.

International Federation of Gynecology and Obstetrics

International classification of cancer of the cervix according to the International Federation of Gynecology and Obstetrics (FIGO) http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-staged

Treatment

After the diagnosis of invasive cervical cancer is established, the decision that has to be made is how to best treat the patient.

Specific therapeutic measures are usually governed by:

- Age and general health of the patient
- Extent of the cancer
- Presence and nature of any complicating abnormalities

It is essential to carry out a complete and careful investigation of the patient, and then a decision regarding treatment should be made by the radiotherapist (if required) and gynecologic oncologist.

The choice of treatment demands clinical judgment; this choice lies frequently between surgery and radiotherapy (almost always given with cisplatin chemotherapy).

In most institutions, the initial method of treatment for locally advanced (stages more advanced than stage I and stage IIA) disease is chemoradiation (cisplatin and radiotherapy), both intracavitary and external radiotherapy.

In general, in early stages, comparable survival rates result from both treatment techniques.

The advantage of radiotherapy is that it is applicable to almost all patients, whereas radical surgery of necessity excludes certain patients who are medically inoperable.

The subject of sexual function after therapy for cervical cancer is often ignored. Patients treated with full pelvic irradiation therapy (i.e., external beam and vaginal brachytherapy) will experience decreased sexual function [3].

Prevention

In 2011 there were 12,710 new cases of invasive cervical cancer and 4290 deaths from this disease in the United States. It is unacceptable that one-third of women diagnosed with cervical cancer will die from this disease that is *largely preventable* by vaccination and screening.

Vaccination

There is no other human malignancy for which we have identified the causative agent, have successfully implemented excellent screening programs, and now have efficacious and tolerable prophylactic vaccination available [3]. There are two US Food and Drug Administration (FDA)-approved vaccines indicated to prevent cervical cancer [3].

Screening

Cytological screening programs (Papanicolau) are effective in reducing mortality from carcinoma of the cervix screening that has decreased the incidence and death rate from cervical cancer, but it also has identified many women with preinvasive neoplasia (which is the role of screening, not to diagnose cancer).

Although the introduction of prophylactic vaccination against HPV would substantially reduce the number of future cases of cervical cancer, the full effect, in terms of a reduction in all ages of cervical cancer incidence, will not be detectable for more than 30 years [6].

The implementation of high-quality screening activities can still potentially play a major role in the prevention of cervical cancer and bridge the gap until the longer-term effects of HPV vaccination programs are seen [4].

Effect on Fertility

More than 30% of cervical cancer patients are diagnosed below the age of 40 years old (13, 14) (1). These young patients diagnosed with cervical cancer often have a strong wish for preserving fertility. Because of the fact that the incidence of cervical cancer in women younger than 40 years is increasing annually in western societies [7], fertility-sparing options of treatment become more important [8].

Cervical cancer is a common indication for hysterectomy. Surgery for cervical cancer is limited to early stages (up to stage IIA), and it usually requires radical hysterectomy, although some patients with early stages can undergo fertility-sparing procedures such as trachelectomy [1, 9, 10].

Fertility Preservation Options

Fertility preservation in young patients with cervical cancer is suitable only for patients with good prognostic factors and disease amenable to surgery without adjuvant therapy.

Consequently, it is only offered to patients with early-stage disease (stage IB tumors <4 cm), negative nodes, and nonaggressive histological subtypes. To determine whether fertility preservation is suitable, the first step is pelvic node dissection to establish nodal spread.

Tumor size (≤2 cm vs >2 cm) and lymphovascular space invasion status are two main factors to determine the best fertility-sparing surgical technique [11].

- In case of FIGO stage IA1 (initial stage of the disease), standard therapy would be extrafascial hysterectomy; if there is desire of fertility preservation, an option maybe a cone biopsy; if it is sufficient, the patient can keep the uterus and achieve pregnancy [3].

- Radical vaginal trachelectomy (RVT) is established as a safe and feasible fertility-sparing procedure for the treatment of patients with early-stage cervical cancer less than 2 cm in diameter, with low morbidity, recurrence, and mortality rates. Five-year disease-free survival rates and overall survival rates of 95% and 97%, respectively, have been reported, making the oncologic outcome of RVT comparable to radical hysterectomy [8].
- Laparoscopic lymphadenectomy followed by neoadjuvant chemotherapy (NACT) and radical vaginal trachelectomy (RVT) in no metastatic disease (pN0) patients with cervical cancer of more than 2 cm seems to be an oncologically safe procedure with promising fertility outcomes. This is a suitable option for women seeking parenthood. The fertility outcome is promising, but premature labor is the main problem [3].
- Uterus transplantation is the first available treatment for absolute uterine infertility, which is caused by the absence of the uterus or the presence of a nonfunctional uterus [12]. *Adoption* would only provide legal motherhood. A *surrogacy arrangement* would provide genetic motherhood and, after adoption of the child from the childbearing mother, also legal motherhood (surrogacy is not legal in many countries). In contrast, UTx mimic a normal situation, with the primary constituents of genetic, gestational, and legal motherhood [1].

References

1. Dahm-Kahler P, Diaz-Garcia C, Brannstrom M. Human uterus transplantation in focus. Br Med Bull. 2016;117(1):69–78.
2. Institute NC. A snapshot of cervical cancer: National Institute of Health; [cited 2014]. Available from: https://www.cancer.gov/research/progress/snapshots/cervical.
3. Tewari KS, Monk BJ. Invasive cervical cancer. J Clin Oncol. 8th ed. Philadelphia: Elsevier/Saunders. 2012:51–119. e13.
4. Vaccarella S, Franceschi S, Zaridze D, Poljak M, Veerus P, Plummer M, et al. Preventable fractions of cervical cancer via effective screening in six Baltic, central, and eastern European countries 2017–40: a population-based study. Lancet Oncol. 2016;17(10):1445–52.
5. Creasman WT. Preinvasive disease of the cervix. J Clin Oncol. 8th ed. Philadelphia: Elsevier/Saunders. 2012:1–30. e6.
6. Van de Velde N, Boily MC, Drolet M, Franco EL, Mayrand MH, Kliewer EV, et al. Population-level impact of the bivalent, quadrivalent, and nonavalent human papillomavirus vaccines: a model-based analysis. J Natl Cancer Inst. 2012;104(22):1712–23.
7. Patel A, Galaal K, Burnley C, Faulkner K, Martin-Hirsch P, Bland MJ, et al. Cervical cancer incidence in young women: a historical and geographic controlled UK regional population study. Br J Cancer. 2012;106(11):1753–9.
8. Lanowska M, Mangler M, Speiser D, Bockholdt C, Schneider A, Kohler C, et al. Radical vaginal trachelectomy after laparoscopic staging and neoadjuvant chemotherapy in women with early-stage cervical cancer over 2 cm: oncologic, fertility, and neonatal outcome in a series of 20 patients. Int J Gynecol Cancer: Off J Int Gynecol Cancer Soc. 2014;24(3):586–93.
9. Dargent D, Martin X, Sacchetoni A, Mathevet P. Laparoscopic vaginal radical trachelectomy: a treatment to preserve the fertility of cervical carcinoma patients. Cancer. 2000;88(8):1877–82.

10. Ungar L, Palfalvi L, Hogg R, Siklos P, Boyle DC, Del Priore G, et al. Abdominal radical trachelectomy: a fertility-preserving option for women with early cervical cancer. BJOG: Int J Obstet Gynaecol. 2005;112(3):366–9.
11. Bentivegna E, Gouy S, Maulard A, Chargari C, Leary A, Morice P. Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review. Lancet Oncol. 2016;17(6):e240–e53.
12. Balayla J, Dahdouh EM, Lefkowitz A. Livebirth after uterus transplantation. Lancet. 2015;385(9985):2351–2.

Index

A
A. *See* Aplastic anemia (AA)
Acute chest syndrome (ACS), 75, 77
Acute lymphoblastic leukemia (ALL)
  age-adjusted incidence rate, 46
  B-cell and T-cell lineages, 48
  clinical manifestations, 46
  definition, 45
  etiology, 45
  fertility, effect on, 49
  fertility preservation options, 49
  incidence, 46
  laboratory findings, 47
  oocyte/embryo cryopreservation, 49
  optimal management, 48
  physical findings, 46–47
  prognostic factors, 47
  risk factors, 47–48
  signs and symptoms, 46
  treatment, 48
Acute myelogenous leukemia (AML)
  clinical manifestations, 41
  definition, 41
  diagnosis, 42
  incidence, 41
  physiopathology, 41
  risk factors, 41
  treatment, 42
Addison's disease, 201
Adrenomyeloneuropathy (AMN), 116–117
Alkylating agents, 189
ALL. *See* Acute lymphoblastic leukemia (ALL)
Alopecia, 235
Alpha-mannosidosis
  disease presentation, 118–119
  fertility, effect on, 119–120
  natural history, 118
  prevalence, 118
AMH. *See* Anti-Mullerian hormone (AMH)
AML. *See* Acute myelogenous leukemia (AML)
Androgen insensitivity syndrome (AIS), 33
  fertility preservation, 33
  gonadal tumors prepuberty, low risk, 33
  gonadectomy after puberty, 33
  partial androgen receptor function, 33
Anti-Mullerian hormone (AMH), 206–207
  PCOS, 236
Antiphospholipid syndrome
  abnormal endovascular trophoblast invasion, 155–156
  clinical criteria for diagnosis, 154
  definition, 153
  diagnosis, 155
  disease presentation, 154–155
  fertility, effect on, 156–157
  laboratory diagnostic criteria, 154
  management, 156
  pathogenesis, 155
  prevalence, 154
Antley–Bixler syndrome, 32
Aplastic anemia (AA)
  acquired forms
    etiology, 82–83
    marrow blood cell production deficiency, 81
    monocytopenia, 81
    neutropenia, 81
    pathophysiology, 82–83
    thrombocytopenia, 81
  bimodal age presentation, 81

A.L. Goetsch et al., *Fertility Preservation and Restoration for Patients with Complex Medical Conditions*, DOI 10.1007/978-3-319-52316-3

Antley (*Cont*)
bone marrow hypocellularity, 81
BTM, 88
chemotherapeutic agents, 90
clinical features, 83
definition, 81
diagnosis, 84–85
differential diagnosis, 85
epidemiology, 81–82
etiology, 82–83
fertility preservation options, 87
HSCT, 87–88
incidence, 82
inherited forms
etiology, 83
Fanconi anemia, 81
pathophysiology, 83
Shwachman–Diamond syndrome, 81
laboratory features
blood findings, 84
pancytopenia, 84
plasma findings, 84
natural history, 84
pathophysiology, 82–83
peripheral blood pancytopenia, 81
physical examination, 83
prognosis, 87
stem cell transplantation, 88
symptoms, 83
TBI therapy, 90
transplantation-related mortality, 89
treatment
bone health, 86
clonal outgrowth, 86
endocrine function, 86
immunotherapy, 86
late effects, 86
serial thyroid monitoring, 86
supportive care, 85–86
Aromatase inhibitors, 278
ART. *See* Assisted reproductive technologies (ART)
Aspartylglucosaminuria (AGU)
disease presentation, 121
fertility, effect on, 121–122
natural history, 120–121
prevalence, 120
Assisted reproductive technologies (ART), 281
Ataxia-telangiectasia (A-T)
cancer susceptibility, 99–100
carrier rate, 99
disease presentation, 97–98
fertility, effect on, 100
incidence, 97
management, 98–99
natural history, 97
Atypical endometrial hyperplasia (AEH), 310–311
Autoimmune digestive disorder. *See* Inflammatory bowel diseases (IBDs)
Autoimmune diseases (AID)
definition, 141
etiology, 141
family planning, 143
fertility and reproduction effect, 143
fertility preservation, 142–143
MG (*see* Myasthenia gravis (MG))
MS (*see* Multiple sclerosis (MS))
POI, 201
prevalence, 141–142
treatment
anti-CD20 monoclonal antibody, 142
chemotherapy, 142
gonadotoxic therapy, 142
Autoimmune polyglandular syndromes (APS)
definition, 162
epidemiology, 162
fertility, effect on, 163
type I, 162
type II, 162–163
type III, 163
type IV, 163
Autoimmune thyroiditis (AIT)
definition, 152
diagnosis, 153
epidemiology, 153
fertility, effect on, 153
prevalence, 153
treatment, 153
Avascular necrosis, 76
Azoospermia, 25, 26, 55, 79, 90, 114

B

Behcet's disease (BD)
clinical manifestations, 152
definition, 152
diagnosis, 152
treatment, 152
BI-RADS. *See* Breast imaging reporting and data system (BI-RADS)
Bone infarction, 76
Bone mineral density (BMD), 203–204
Borderline malignant neoplasms (BOT)
definition, 295

epidemiology, 295
incidence, 295
treatment, 295–296
Breast cancer
diagnostic evaluation and techniques
fine-needle aspiration/biopsy, 275
image-guided percutaneous breast biopsy, 276
mammography, 275
MRI, 276–277
needle localization and excision, 275
palpable mass, 275
stereotactic biopsy, 276
ultrasound-guided biopsy, 276
fertility, effect on
fertility preservation, 281–283
systemic therapy and reproductive system, 281
incidence, 269–270
natural history, 270
pathology, 273–274
risk factors
environmental factors, 272
protective factors, 273
screening
mammography, 274–275
palpable mass, 274
staging, 273
treatment
breast reconstruction, 279–280
gene expression assays, 279
local therapy, 277–278
metastatic disease, 279
neoadjuvant chemotherapy, 279
radiation therapy, 279
systemic therapy, 278
Breast imaging reporting and data system (BI-RADS), 274–275
Breast-ovarian cancer syndrome, 290
β-Thalassemia major (BTM)
assisted reproductive techniques, females, 69
blood transfusion, 68
BMT, 88
endocrine complications, 68
epidemiology, 64
hormone replacement therapy, pregnancy, 69
hypogonadism, 68
intensive iron chelation therapy, 68, 69
laboratory features, 67
in male patients, 70
management, 69
osteoporosis, 68
quality of life, 69
severe anemia, 68

C
Carpenter's syndrome, 162
Cervical cancer
clinical manifestations, 324
diagnosis, 324–325
fertility, effect on, 327
fertility preservation, 327–328
histologic classification
epithelial tumors, 322–323
nonepithelial tumors, 323
natural history, 321–322
prevention
cytological screening programs, 327
vaccination, 326
risk factors, 323–324
staging, 325
symptoms/indicators, 324
treatment, 326
Cervical dysplasia, 256
Cervical intraepithelial neoplasia (CIN), 322, 325
Chemotherapy-related amenorrhea (CRA), 281
Cholesterol ester storage disease (CESD), 129–131
Chronic kidney disease (CKD)
abnormal smear test, 186
causes, evaluation of, 184
clinical manifestations, 182
contraception, 186–187
cyclophosphamide, 187–188
definition, 181
epidemiology, 183
ESRD (*see* End-stage renal disease (ESRD))
etiology, 183
fertility
men on dialysis, 193
preservation options, 188–190
women on dialysis, 192–193
immunosuppression, 192
incidence, 182
maternal complications, 186
nephrotic syndrome, 190–191
physiopathology, 182
risk factors, 181–182
sexual effects, 191–192
stages, 183
treatment, 184

Chronic lymphocytic leukemia (CLL)
clinical progression, 50
definition, 49
diagnosis, 51
disease presentation, 50–51
epidemiology, 50
etiology, 49
fertility, effect on, 52
incidence, 50
laboratory features, 51
treatment, 51
Chronic myelogenous leukemia (CML)
age-specific incidence rate, 43
bone marrow morphology, 44
clinical manifestations, 43–44
definition, 42–43
epidemiology, 43
fertility, effect on, 44
fertility preservation methods, 44–45
laboratory findings, 44
natural history, 43
physical examination, 44
symptoms, 43
treatment, 44
CIN. *See* Cervical intraepithelial neoplasia (CIN)
CKD. *See* Chronic kidney disease (CKD)
CLL. *See* Chronic lymphocytic leukemia (CLL)
Clomiphene citrate (CC), 244, 245, 289
CML. *See* Chronic myelogenous leukemia (CML)
Congenital adrenal hyperplasia (CAH)
biallelic pathogenic variants, 30
diagnosis and treatment, 31
21-hydroxylase deficiency, 30, 31
newborn screening, 31
salt-wasting type, 31
signs and symptoms, 31
virilized external genitalia, 30
Cooley anemia. *See* β-Thalassemia major (BTM)
Cowden syndrome, 13, 306
Crohn's disease (CD), 252
Cumulus-oocyte complexes (COCs), 282
Cyclophosphamide, 184, 187–188

D
Danazol, 220
Deficient ovarian reserve (DOR), 206
Dialysis, fertility
in men, 193
in women, 192–193
Digestive autoimmune diseases
CD, 252
definition, 251
diagnosis, 252
etiology and pathophysiology
environmental factors, 253–254
genetics, 253
immune system, 254
fertility, effect on
fertility preservation, 262–263
IVF, 262
male fertility, 262
pregnancy outcomes, 261
management, 257
medical treatment, 258
presentation
abscess, 256
cervical dysplasia, 256
fistula, 256
gastrointestinal symptoms and extraintestinal symptoms, 254–255
menstrual cycle, gastrointestinal symptoms to, 255
psychological aspects, 255
stricture, 256
toxic megacolon, 257
surgery, 258–259
UC, 252
Disorders of sexual development (DSD)
AIS, 27, 33
atypical genitalia, 27
carcinoma in situ, 28
chromosome abnormalities, 28
fertility preservation, 28
genetic etiology and inheritance, 28
gonadal dysgenesis, 27, 28, 29
gonadectomy, 28
gonadoblastoma, 28
Klinefelter syndrome (*see* Klinefelter syndrome)
medical management, 28
mixed gonadal dysgenesis, 21–22, 27
ovotesticular, 28–30
PGD, 28
PGS, 28
testosterone biosynthesis defects, 27, 30–32
TS (*see* Turner syndrome)
Dyslipidemia, 238

E
Endometrial cancer (EC)
clinical manifestations, 306
definition, 303
diagnosis
endometrial biopsy, 307
fractional dilation and curettage, 307
hysteroscopy, 307
pathology, 308
ultrasonography, 307–308
uterine adenocarcinoma screening, 306
epidemiology, 303–304
etiology, 305–306
fertility, effect on, 313
fertility preservation
assisted reproductive technologies, 316
cancer recurrence, 313
fertility-sparing procedures, 313
fertility-sparing surgical procedures, 314
hormonal treatment, 314
hysteroscopic control, 315
progestin usage, 314
spontaneous conception, 315
tumor histological type, 314
2009 FIGO Staging System, 308
follow-up, 312–313
incidence, 303
management
chemotherapy, 312
radiation therapy, 312
surgical treatment, 311–312
natural history
type 1, 304
type 2, 304–305
pathogenic types, 304
prevention of
lifestyle modifications, 309–310
oral contraceptives, 310
periodic exposure to progestins, 310
prognostic factors, 309
subtypes, 308–309
treatment
AEH management, 310–311
hyperplasia without atypia management, 311
tumor grade, 309
Endometriosis
classification, 219
definition, 217
diagnosis, 218–219
disease presentation, 218
fertility, effect on, 222
incidence, 217
lifestyle and dietary interventions, 220
management, 219
medical treatment, 220–221
natural history, 217–218
preservation, fertility, 222–223
surgical treatment, 221
End-stage renal disease (ESRD)
fertility, women with, 185–186
risk factors, 183–184
Epithelial ovarian cancer (EOC), 14, 288, 289, 291, 293–297
Epithelial tumors
glandular, 323
nonglandular, 322–323
ESRD. *See* End-stage renal disease (ESRD)
Estrogen receptor-positive breast cancer, 278

F
Family building options, alternative
adoption, 5
donor eggs, 5
donor embryos, 5
donor sperm, 5
Female fertility preservation
cryopreservation
embryo, 3
oocyte, 3–4
ovarian tissue, 4
effect
APS, 146
drug-related infertility, 146
lupus nephritis, 146
menstrual disturbances, 145–146
reproductive system impairment, 146
egg banking, 3–4
embryo banking, 3
ovarian suppression, 4
SLE
gonadotrophic receptor hormone agonist, 147
oocyte and embryo cryopreservation, 147–148
ovarian tissue cryopreservation, 148
Fertility preservation techniques
AA, 87
ALL, 49
CKD, 188–190
CML, 44–45
female (*see* Female fertility preservation)
HL, 55–56
HSCT, 114–115

Fertility preservation techniques (*Cont*)
male (*see* Male fertility preservation)
NHL, 57
POI, 208–209
SLE, 148–149
TS, 22–23
Fertility-sparing surgery (FSS), 297–298
Fistula, 256
Follicle depletion, 198
Fragile X-associated primary ovarian insufficiency (FXPOI)
diagnosis, 101–102
disease presentation, 102
emotional well-being, 103
family planning considerations, 103
fertility, effect on, 102–103
fragile X carrier testing, 103
natural history, 101
prevalence, 100–101
Fragile X-associated tremor/ataxia syndrome (FXTAS), 101, 102
Fucosidosis
disease presentation, 122–123
fertility, effect on, 123
natural history, 122
prevalence, 122

G
Galactosemia
disease presentation, 104
fertility, effect on
fertility preservation, expert opinion, 105–106
primary ovarian insufficiency, 104
spontaneous pregnancies, 105
natural history, 104
prevalence, 103
GAPO syndrome, 106
Gaucher disease
disease presentation
type I, 124
type II, 124
type III, 124
fertility, effect on, 124
natural history, 123
prevalence, 123
Gene expression assays, 279
Genetic disorders, gonadal dysfunction
A-T (*see* (Ataxia-telangiectasia (A-T)))
FXPOI (*see* (Fragile X-associated primary ovarian insufficiency (FXPOI)))
galactosemia (*see* (Galactosemia))
GAPO syndrome, 106
22q11.2 Deletion Syndrome, 106–108
Genitourinary systems, 75
Globoid cell leukodystrophy, 128–129
Gonadal dysgenesis
complete and partial, 27
mixed, 27
single-gene disorders, 28, 29
Gonadotropin-releasing hormone (GnRH) agonists, 283
Gonadotropin secretion, abnormal, 237, 240
Graft-*versus*-host disease (GVHD), 85, 88–91
Gynecologic hereditary cancer predisposition syndromes
Cowden syndrome, 13
HBOC (*see* Hereditary breast and ovarian cancer (HBOC))
hereditary leiomyomatosis, 14
Li–Fraumeni syndrome (LFS), 13
Lynch syndrome (*see* Lynch syndrome)
PJS, 13
renal cell carcinoma, 14

H
Hematologic malignancies (HMs)
leukemia, 39–40
lymphoid diseases
ALL, 45–49
CLL, 49–52
HL (*see* Hodgkin lymphoma (HL))
lymphoma, 52
NHL (*see* Non-Hodgkin lymphoma (NHL))
myeloid diseases
AML, 41–42
CML, 42–45
patients, survival rates, 39
Hematopoietic stem cell transplantation (HSCT)
AA patients, 87
curative treatment, 87
female fertility, 114
fertility preservation methods, 44, 114–115
gonadotoxic medications, 113
immune deficiencies, 87
inborn errors of metabolism, 87
limited safety, 113
male fertility, 114
myeloablative conditioning regimens, 80, 90
myeloid and lymphoid malignancies, 87
pregnancy rates, 91

procedure-related morbidity and mortality, 113
SAA, treatment, 85
SCD-related morbidity, 78
structural hemoglobinopathies, 88
treatment-induced infertility in leukemia, 49
Hemodialysis (HD), 185
Hemoglobinopathies
definition, 61–62
prevalence, 62
SCA (*see* (Sickle cell anemia (SCA)))
thalassemia syndromes (*see* (Thalassemia))
Hereditary breast and ovarian cancer (HBOC)
autosomal dominant genetic disorder, 9
BRCA1/2 mutations
early oocyte apoptosis and depletion, 9
IVF, 9
lifetime cancer risks, 7, 8
embryo selection, 9
PGD, 9
Hereditary leiomyomatosis, 14
Hereditary nonpolyposis colon cancer (HNPCC), 10, 11, 306. *See also* Lynch syndrome
Hereditary ovarian cancer, 290–291
Hirsutism, 235
Hodgkin lymphoma (HL)
anthracycline-containing chemotherapy, 55
clinical manifestations, 53–54
cryopreservation and reimplantation, ovarian cortex, 56
definition, 52–53
embryo/oocyte cryopreservation, 56
etiology, 54
fertility issues and preservation methods, 55–56
genetic susceptibility and familial aggregation, 54
incidence, 53
involved-field radiotherapy, 55
limited-stage disease, 55
mononucleosis infection, 54
prognosis, 53, 55
treatment, 54–55
Hormone replacement therapy (HRT), 8, 204–206, 271
Human leukocyte antigen-matched sibling donors (HLA-MSD)
HCT, 89
SCD, 88
Hunter syndrome
disease presentation, 125
fertility, effect on, 125–126
natural history, 124–125
prevalence, 124
Hurler–Scheie syndrome, 127
Hurler syndrome
disease presentation, 126–127
fertility, effect on, 127–128
natural history, 126
prevalence, 126
Hyperandrogenism
biochemical, 234–235
causes, 234
clinical evidence, 234
PCOS, 243
Hyperplasia without atypia management, 311

I

IBDs. *See* Inflammatory bowel diseases (IBDs)
Immune system, 254
Immunosuppression, 117–118, 192, 256, 258
Inborn errors of metabolism (IEMs)
AGU, 120–122
alpha-mannosidosis, 118–120
fucosidosis, 122–123
Gaucher disease, 123–124
HSCT, 113–115
Hunter syndrome, 124–126
Hurler syndrome, 126–128
I-cell disease, 133–134
Krabbe disease, 128–129
LAL deficiency, 129–131
Maroteaux–Lamy syndrome, 131–132
Morquio syndrome, 132–133
Mucolipidosis II, 133–134
Sanfilippo syndrome, 134–135
Sly syndrome, 135–136
X-ALD, 115–118
Inflammatory bowel diseases (IBDs)
CD, 252
definition, 251
diagnosis, 252
etiology and pathophysiology
environmental factors, 253–254
genetics, 253
immune system, 254
fertility, effect on
fertility preservation, 262–263
IVF, 262
male fertility, 262
pregnancy outcomes, 261
management, 257

Inborn (*Cont*)
medical treatment, 258
presentation
abscess, 256
cervical dysplasia, 256
fistula, 256
gastrointestinal symptoms and extraintestinal symptoms, 254–255
menstrual cycle, gastrointestinal symptoms to, 255
psychological aspects, 255
stricture, 256
toxic megacolon, 257
surgery, 258–259
UC, 252
Insulin resistance, 238
Intracytoplasmic sperm injection (ICSI)., 2
Intrauterine insemination (IUI), 222
In vitro fertilization (IVF), 262
In vitro maturation (IVM), 49, 57, 245, 246, 282
IUI. *See* Intrauterine insemination (IUI)

K
Kidney transplantation (KT), 185, 189
Klinefelter syndrome
disease presentation, 24
fertility, effect on, 24
fertility preservation, 24
signs and symptoms, 24
sperm retrieval, 24
Krabbe disease
disease presentation, 128
fertility, effect on, 129
natural history, 128
prevalence, 128

L
Letrozole, 244–245
Leukemia
definition, 39
epidemiology, 40
incidence, 40
risk factors, 40
Li–Fraumeni syndrome (LFS), 13
Lymphoid diseases
ALL, 45–49
CLL, 49–52
HL, 52–56
lymphoma, 52
NHL, 56–57
Lymphoma
HL (*see* (Hodgkin lymphoma (HL)))
incidence, 52
mortality, 52
NHL, 56–57
risk factors, 52
treatments, 52
Lynch syndrome
assisted reproductive technologies, 13
cancer risk-reducing strategy, 11
diagnosis, 12
endometrial cancer, 11
hormone replacement therapy, 12
lifetime cancer risks, 10
ovarian cancer, 11
PGD, 12
prenatal testing, 12
prophylactic hysterectomy, 12
prophylactic surgery, premenopausal women, 12
revised Bethesda guidelines, 10
revised guidelines, 12
Lysosomal acid lipase (LAL) deficiency
disease presentation, 129–130
fertility, effect on, 130–131
natural history, 129
prevalence, 129

M
Male fertility preservation
effect on
autoimmune orchitis, 147
drug-related infertility, 147
Klinefelter syndrome, 147
reproductive system impairment, 147
experimental techniques, 1
gonadal shielding, 2
semen cryopreservation, 1
SLE
sperm banking, 148
testicular tissue banking, 148
testosterone, 148
sperm banking, 1
testicular tissue cryopreservation, 2
in vitro SSC culture, 2, 3
Maroteaux–Lamy syndrome
disease presentation, 132
fertility, effect on, 132
natural history, 131
prevalence, 131
Matched sibling donors (MSD), nonmalignant late complications, 87

Mayer–Rokitansky–Kuster–Hauser syndrome, 108
Menstrual dysfunction, 235–236
Metabolic syndrome (MetS), 239
Metastatic disease, 279
Metformin, 245
Morquio syndrome
  disease presentation, 133
  fertility, effect on, 133
  natural history, 132
  prevalence, 132
Mucolipidosis II
  disease presentation, 134
  fertility, effect on, 134
  natural history, 133
  prevalence, 133
Mucopolysaccharidosis (MPS)
  type I (*see* (Hurler syndrome; Scheie syndrome))
  type II (*see* (Hunter syndrome))
  type III (*see* (Sanfilippo syndrome))
  type IV (*see* (Morquio syndrome))
  type VI (*see* (Maroteaux–Lamy syndrome))
  type VII (*see* (Sly syndrome))
Multiple sclerosis (MS)
  clinical course, 174
  definition, 173
  epidemiology, 173
  fertility, effect on
    AIT, 177
    assisted reproduction techniques, 176, 177
    cyclophosphamide, 176
    epigenetic factors, 175
    female-to-male ratio, 174
    fingolimod, 175
    gene–environment interactions, 175
    hormonal alteration, 177
    interferon and glatiramer acetate, 175
    mitoxantrone, 176
    natalizumab, 175
    transvaginal ultrasound, 176
  incidence, 177
  natural history, 174
  treatment, 174
Musculoskeletal system, 75, 126, 158
Myasthenia gravis (MG)
  clinical presentation, 172
  definition, 171
  diagnostic tests, 172
  fertility, effect on, 173
  incidence, 171
  myasthenia, 171
  physiopathology, 171
  prevalence, 171
  treatment, 173
Mycophenolate mofetil (MMF), 189
Myeloid diseases
  AML, 41–42
  CML, 42–45

N

Nephrotic syndrome, 190–191
NHL. *See* Non-Hodgkin lymphoma (NHL)
Nocturnal enuresis, 75
Node-positive breast cancer, 278
Non-Hodgkin lymphoma (NHL)
  fertility, effect on, 56
  fertility preservation options, 57
  forms of, 56
  incidence, 56
  risk of, 56
  survival rates, 56
  treatment modalities, 56
  treatment protocols, 57
Nonmalignant hematologic diseases
  AA (*see* (Aplastic anemia (AA)))
  hemoglobinopathies, 61–62
  SCD (*see* (Sickle cell disease (SCD)))
  thalassemia, 62–71
Normspermia, 25, 26

O

Obesity, 238–239
Oligospermia, 25, 26, 190
Osteomyelitis, 76
Osteopenia, 76, 86, 156
Osteoporosis, 12, 67, 68, 76, 188, 204, 295
Ovarian cancer
  BOT
    definition, 295
    epidemiology, 295
    incidence, 295
    treatment, 295–296
  clinical manifestations
    benign disease elements, 292
    malignant disease elements, 292
    serological biomarkers, 292
    symptoms, 291–292
    ultrasound, 292
  definition, 287
  diagnosis, 291
  differential diagnosis, 292–293

Ovarian cancer (*Cont*)
etiology, 289–290
fertility preservation
conservative surgery, 297
EOC, 296
FSS, 297–298
patients with negative tumor markers, 298–299
pediatric and adolescent ovarian lesions, management, 298
hereditary ovarian cancer, 290–291
incidence and mortality, 287–288
risk factors, 288
staging
guidelines, 293
survival, 293
treatments, 294–295
Ovarian tissue cryopreservation (OTC), 80, 208
Ovotesticular disorders of sexual development
7-alpha-hydroxlase, 31
5-alpha reductase enzyme, 32
3-beta hydroxysteroid dehydrogenase, 31
cytochrome P450 oxidoreductase, 31–32
gonadectomy, 29–30
17-ketosteroid reductase, 32
steroid 17-alpha-monooxygenase, 31
Ovulatory dysfunction, 235–236

P
PCOS. *See* Polycystic ovary syndrome (PCOS)
Peutz–Jeghers syndrome (PJS), 13
POI. *See* Premature ovarian insufficiency (POI)
Polycystic ovary syndrome (PCOS)
definition, 233
diagnosis
in adolescents, 242
evaluation with, 241
Rotterdam consensus, 241
fertility, effect on, 240
incidence, 233
management
hyperandrogenism, 243
immediate and longer-term clinical consequences, 242
lifestyle and dietary interventions, 243
menstrual abnormalities, 243
T2D, risk for, 244
natural history, 234
pathophysiology, 240
preconceptional issues and infertility treatment
CC, 244
combined treatment with CC and metformin, 245
first-line treatment, 244
letrozole, 244–245
recombinant FSH, 245
second-line medical treatment, 245
presentation
abnormal gonadotropin secretion, 237
acne, 235
alopecia, 235
cancer risks, 239–240
clinical expression, 234
dyslipidemia, 238
hirsutism, 235
hyperandrogenism, 234–235
insulin resistance, 238
mental health, effect on, 239
metabolic abnormalities and associated health risks, 239
obesity, 238–239
ovulatory and menstrual dysfunction, 235–236
polycystic ovaries, 237
preservation, fertility, 246
Preimplantation genetic diagnosis (PGD), 28
A-T, 100
emotional impact, 9
HBOC patient, 9
Lynch syndrome, 12, 13
22q11.2 deletion syndrome, 109
in vitro fertilization, 109
X-ALD, 118
X chromosome abnormalities, 27
Premature ovarian insufficiency (POI)
definition, 197–198
diagnosis
autoimmune diseases, 201
cancer treatments, 201–202
causes, 200
chemotherapy, 202
genetic disorders, 200–201
laboratory evaluation, 199–200
physical examination, 199
radiotherapy, 202
disease presentation, 199
etiology, 198
fertility, effect on, 206–208
fertility preservation, 208–209
HRT, 205–206
incidence, 197

management
bone protection and improvement, 203–204
cardiovascular system protection, 204
consequences, treatment for, 205
genitourinary symptoms, treatment of, 205
lifestyle and dietary interventions, 204–205
natural history, 198
Priapism, 75, 78
Prophylactic bilateral salpingo-oophorectomy (PBSO)
cancer risk reduction, 8, 11
immediate menopause, 8
ovarian cancer prevention strategy, 7

R
Recombinant follicle-stimulating hormone, 245
Rheumatic diseases
AIT, 152–153
antiphospholipid syndrome, 153–157
APS, 162–163
BD, 152
RA, 149–151
scleroderma, 160–162
SLE, 144–149
SS, 157–160
symptoms, 144
vasculitis, 151
Rheumatoid arthritis (RA)
autoreactivity, 150
clinical manifestations, 150
clinical synovitis, 150
diagnosis, 150
epidemiology, 149
etiology, 149
fertility, effect on, 150–151
genetic features, 149
infertility
iatrogenic causes, 151
medications, 151
pain, 150

S
Sanfilippo syndrome
disease presentation, 134–135
fertility, effect on, 135
natural history, 134
prevalence, 134
Scheie syndrome, 126–127
Schmidt's syndrome, 162
Scleroderma
clinical manifestations, 161
definition, 160
diagnosis, 161
early symptoms, 161
environmental/genetic factors, 161
epidemiology, 160
ethiopatogenia, 160–161
fertility, effect on, 162
pathogenesis, 160
prevalence, 160
progressive connective tissue disease, 161
severe vasospasm, 161
vascular occlusive changes, 161
Septic arthritis, 76
Serous adenocarcinoma (SC), 308
Sex chromosome disorders. *See also* Disorders of sexual development (DSD)
karyotype, 200
Klinefelter syndrome (*see* (Klinefelter syndrome))
TS (*see* (Turner syndrome (TS)))
Y chromosome infertility (*see* (Y chromosome-related azoospermia))
Shwachman–Diamond syndrome, 81
Sickle cell anemia (SCA)
BMT, 90
diminished ovarian reserve, 79
gene therapy, 70
gonadotoxicity, 79
hydroxyurea, 79, 80
premature ovarian insufficiency, 79
prevalence, 72
progressive organ damage, 72
shortened life span, 72
Sickle cell disease (SCD)
BMT, 79
clinical manifestations
aplastic crises, 74
avascular necrosis, 76
bone infarction, 76
cardiac manifestations, 75
chronic and progressive, 73
genitourinary systems, 75
hyperhemolytic crisis, 74
musculoskeletal system, 75
nocturnal enuresis, 75
ophthalmic complications, 76
osteomyelitis, 76
osteopenia, 76
osteoporosis, 76

Sickle cell disease (*Cont*)
pain, acute/chronic, 74
priapism, 75
pulmonary manifestations, 75
retinopathy, 76
septic arthritis, 76
sequestration crises, 74
sickle cell crises, 74
splenic complications, 76
stroke, 75
vasoocclusion, 76
vaso-occlusive crises, 74
course and prognosis, 73
cryopreservation
of mature oocytes, 80
of sperm, 80
of testicular tissue, 80
definition, 71–72
effect, fertility
clinical characteristics, 78
hydroxyurea therapy, 78–79
laboratory findings, 78
long-term therapies, 78
in men, 78
patient counselling, 77
reproductive issues, 78
sperm abnormalities, 78
transfusional iron overload, 78
epidemiology, 72
fertility preservation, 79–81
hypogonadism exacerbation, 80
laboratory features, 73
myeloablative conditioning regimens, 80
pathophysiology, 72–73
treatment
acute red cell transfusion, 77
chronic transfusion, 77
fetal hemoglobin levels, 76
gene therapy, 77
hydroxyurea, 77
pain control, 77
transfusion, 76
Sickle cell retinopathy, 76
Sjögren's syndrome (SS)
clinical features
endocrine involvement, 159
gastrointestinal and hepatobiliary manifestations, 158
lymphoproliferative disease, 159
musculoskeletal non-erosive arthritis, 158
neuropsychiatric involvement, 159
Raynaud's phenomenon, 158
renal involvement, 158
respiratory tract involvement, 158
vasculitis, 158
definition, 157
diagnosis, 159
differential diagnosis, 159
etiology, 158
fertility, effect on, 160
incidence, 157
pathogenesis, 158
treatment, 159–160
Sly syndrome
disease presentation, 135–136
fertility, effect on, 136
natural history, 135
prevalence, 135
Smear test, abnormal, 186
Spermatogonial stem cells (SSCs), 191
normal spermatogenesis, 2
spermatozoa maturation, testicular tissue organ culture, 2
testicular tissue autografting/xenografting, 2
Sperm banking, 1, 80, 148, 190
Stem cell transplantation, 42, 70, 88
Systemic lupus erythematosus (SLE)
disease presentation, 144
female fertility, effect on
APS, 146
drug-related infertility, 146
lupus nephritis, 146
menstrual disturbances, 145–146
reproductive system impairment, 146
fertility preservation expert opinion, 148–149
male fertility, effect on
autoimmune orchitis, 147
drug-related infertility, 147
Klinefelter syndrome, 147
reproductive system impairment, 147
natural history, 144
prevalence, 144

T
Tamoxifen, 278
T2D. *See* Type 2 diabetes (T2D)
Testicular biopsy, 191
Testicular feminization syndrome. *See* Androgen insensitivity syndrome (AIS)

Testicular sperm extraction (TESE), 2
Testicular tissue banking, 148
Testosterone biosynthesis defects
  adrenal insufficiency, 30
  enzymes, 30
  fertility preservation, 30
  gonadal tumors, risk of, 30
  steroidogenic acute regulatory protein, 30
Thalassemia
  α-thalassemia, 62
  β-thalassemia
    BTM, 62–63
    thalassemia intermedia, 63
    thalassemia minor/minima, 63
  clinical manifestations
    abnormal iron metabolism, 66–67
    β-globinopathy-affected infants, 65
    clinical severity, 64
    genetic and environmental factors, 64
    globin-chain imbalance, 64
    gross splenomegaly, 65
    postsplenectomy infections, 65–66
    splenectomy, 65–66
    tissue hypoxia, 65
    transfusion program, 65
  definition, 62
  differential diagnosis, 67
  epidemiology, 64
  iron overload, fertility effect
    blood transfusion, 68
    in female, 69
    gene therapy, 70–71
    hypogonadism, 68
    iron chelation, 70
    in male, 70
    stem cell transplantation, 70
  laboratory features, 67
  pathophysiology, 64
  prevention, 71
  prognosis, 71
  treatment
    general care, 67–68
    transfusion, 68
Toxic megacolon, 257
Turner syndrome (TS)
  disease presentation, 20
  fertility preservation research, 22–23
  fetal chromosome abnormalities, 21
  incidence, 19
  limited reproductive options, 21
  with mixed gonadal dysgenesis, 21–22
  monosomy, 19
  mosaicism, 19
  natural history, 19–20
  ovarian failure, 20–21
22q11.2 deletion syndrome
  diagnosis, 107
  disease presentation, 107–108
  fertility, effect on, 108–109
  natural history, 106
  prevalence, 106
Type 2 diabetes (T2D), 66, 201, 234, 238, 242, 244, 305

U
UAE. *See* Uterine artery embolization (UAE)
Ulcerous colitis (UC), 251, 252
Uterine artery embolization (UAE), 230
Uterine fibroids
  clinical manifestations, 228
  fertility, effect on, 228–230
  natural history, 228
  prevalence, 227
  risk factors, 227
Uterine papillary serous carcinoma (UPSC), 308
Uterovaginal aplasia, 108

V
Vasculitis, 151

W
Wolman disease, 129–131

X
X chromosome deletions and balanced translocations
  in female infertility, 27
  in male infertility, 26–27
X-linked adrenoleukodystrophy (X-ALD)
  adrenocortical insufficiency, 117
  AMN, 116–117
  asymptomatic and presymptomatic individuals, 117
  cerebral form, 116
  disease presentation, 116
  female carriers, 117
  fertility, effect on, 117–118
  natural history, 115
  PGD, 118
  prenatal testing, 118
  subtypes, 116

Y
Y chromosome-related azoospermia
disease presentation, 25–26
familial microdeletion, 26
infertile/subfertile sons, 26
infertility types, 26
natural history, 25
prevalence, 25