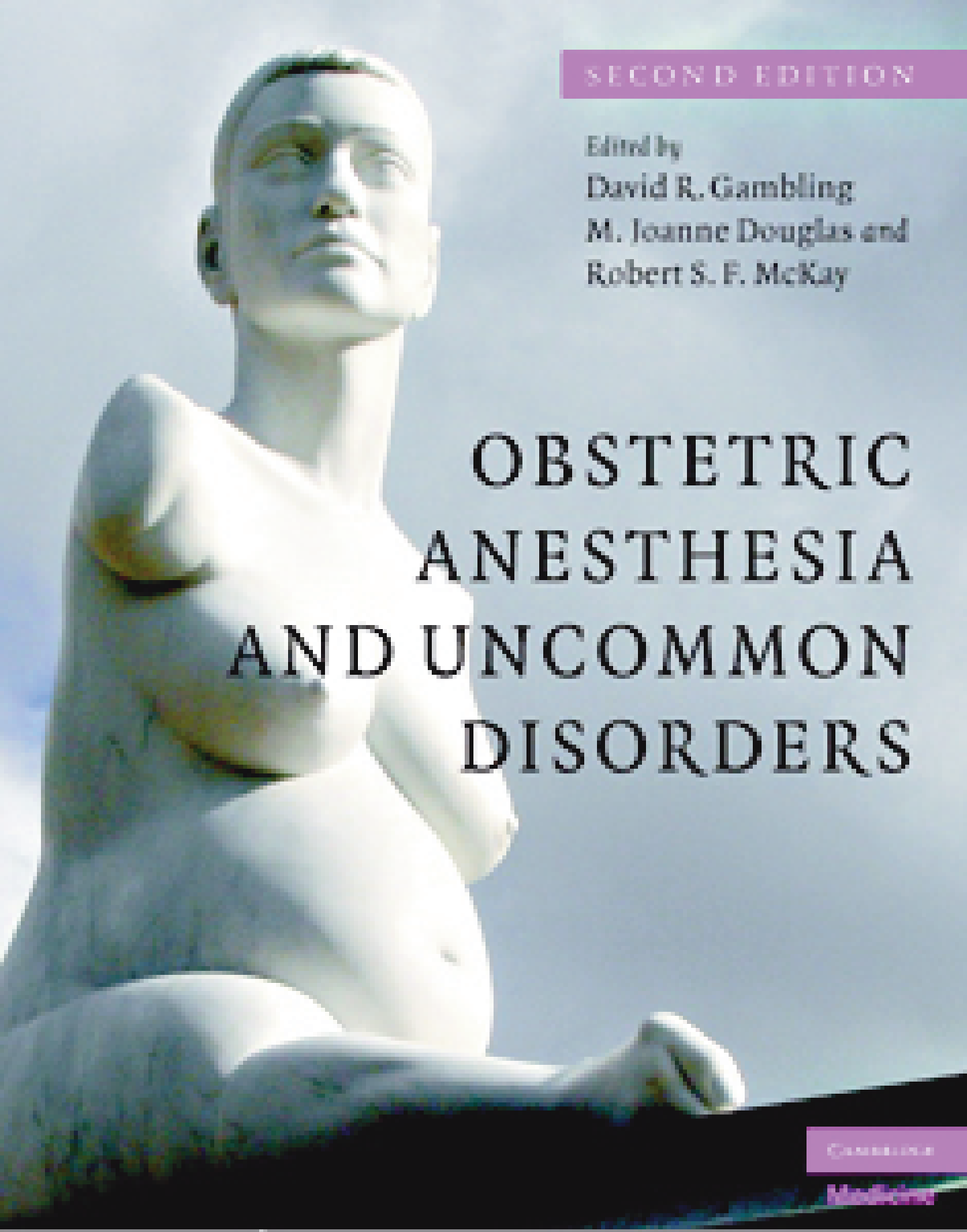

SECOND EDITION

Edited by
David R. Gambling
M. Joanne Douglas and
Robert S. F. McKay

OBSTETRIC ANESTHESIA AND UNCOMMON DISORDERS

Cambridge Medicine

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Obstetric Anesthesia and Uncommon Disorders, 2nd edition

This new edition of *Obstetric Anesthesia and Uncommon Disorders* provides a convenient resource for practitioners suddenly faced with a parturient who has an unusual medical or surgical condition.

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International Journal of Obstetric Anesthesia

"... covering conditions as diverse as cystic fibrosis, acute severe asthma, rheumatoid arthritis, and transplants... it is a must for every delivery suite." *British Journal of Anaesthesia*

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2nd edition

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PREFACE TO THE SECOND EDITION

It has been almost ten years since the first edition of *Obstetric Anesthesia and Uncommon Disorders* was published. Over the past few years colleagues have asked the editors when they could expect to see a new edition. We had some hesitation, not least of which was because we felt that many practioners could find most of this information for themselves using the internet or subspecialty journals. Upon reflection, we recognized that there is no substitute for a textbook that contains information gathered and carefully reviewed by a number of devoted specialists. Hence, spurred on by those requests for a second edition it was decided to create a revision that provides more recent references and reflects some of the changes in obstetric anesthesia practice that have occurred over the past ten years. With the assistance of a third editor, Robert S. F. McKay, we recruited some outstanding new contributors from around the world and created a second edition that we trust the reader will find useful. We have continued to use chapters based on body systems and diseases. We have consolidated some chapters, split others, and added two new chapters, namely 'Chronic pain in pregnancy' and 'Malignancy and pregnancy'. There are now 23 chapters each illustrated with figures, tables, and photographs, and each chapter is accompanied by a comprehensive list of updated references.

We thank our new publishers, Cambridge University Press, for giving us the opportunity to produce this revision, and we would like to thank each and every contributor for their hard work and commitment to this project.

Finally, we want to thank our families for their patience while we spent hours, too numerous to count, fine tuning each chapter.

This book is dedicated to my wife Kimberley and children Carwyn, Jake, and Samantha. David R. Gambling

This book is dedicated to my family: my mother, Bill, Matthew, Sheila, Erin, and Mark, who fill my life with joy.

M. Joanne Douglas

We dedicate this book to the many anesthesiologists who work long hours to provide safe care to mothers and babies, and to their families who make the sacrifices that allow their loved one to provide this care. Thank you Susan, Lindsey, and Katie.

Robert S. F. McKay

To the memory of Dr Clive Meintjies a wonderful friend, mentor and doctor.

1 STRUCTURAL HEART DISEASE IN PREGNANT WOMEN

Brendan Carvalho and Ethan Jackson

Introduction

This chapter will outline the physiological changes, hemodynamic goals, management, and anesthetic options with regards to patients with acquired or congenital structural heart disease during pregnancy, labor, and delivery. There is no consensus as to the optimal anesthetic technique for the conditions being discussed. General and regional anesthesia can have significant cardiovascular effects on a parturient with cardiac disease. In addition, many pharmacological agents commonly used in anesthetic and obstetric practice can have adverse hemodynamic effects (Table 1.1).

Due to the nature and the rarity of the cardiac diseases discussed, there is a lack of randomized controlled studies to guide our practice. As a result, case reports and expert opinion will form the basis of discussing the anesthetic techniques. However, management options and anesthetic techniques must be individualized and based on the prevailing hemodynamic condition and obstetric needs.

Scope of the problem

An estimated 0.2–3.0% of pregnant patients have cardiac disease,[1] an increasing cause of maternal mortality.[2,3] The 2000–2 *Confidential Enquiries into Maternal Deaths in the United Kingdom* reported that cardiac disease was the second most common nonobstetric cause of maternal death after psychiatric disease.[4] Cardiac disease is also more common than the leading direct causes of maternal death.[4,5] The maternal mortality rate ranges from 0.4% in New York Heart Association (NYHA) class I–II women to 6.8% in class III–IV (Tables 1.2 and 1.3). Despite a dramatic decline over the last few decades in the incidence of rheumatic heart disease among women of childbearing age in the developed world, more women with partially or fully corrected congenital heart disease (CHD) are surviving to reproductive age because of improved surgical techniques and advances in medical management.[6,7]

The principal danger for a pregnant woman with a heart lesion is cardiac decompensation because of the inability to meet the additional demands imposed by the physiological changes of pregnancy and parturition. In addition, infection, hemorrhage, and thromboembolism can compound the risk. Maternal and neonatal outcomes can both be improved by meticulous peripartum care. However, some women with serious cardiac disease may still suffer significant morbidity and mortality despite optimal medical care.[4,8]

Physiology of pregnancy

A comparison between normal cardiopulmonary parameters in the pregnant and nonpregnant states is shown in Table 1.4. Pregnancy exerts a progressive cardiovascular stress that peaks at approximately 28–32 weeks of gestation.[9] Cardiac output (CO) starts to increase by the tenth week of gestation and continues to rise to a peak of 30–50% above baseline by 32 weeks' gestation. The increase in CO is due to increased stroke volume (SV) – up to 30% above baseline – in the first half of pregnancy. This is in contrast to the latter half of pregnancy when CO is maintained by an increase in heart rate (HR) – up to 15% above baseline – in addition to the increased SV. Plasma volume increases by 40–50% from prepregnant levels. This raised plasma volume exceeds the increase in red blood cells resulting in a relative anemia that may compromise oxygen delivery. Blood pressure (BP) usually falls during pregnancy due to progesterone-induced vasodilatation and the low resistance placental bed. Pulse pressure widens due to a greater reduction in diastolic BP compared to systolic BP.

Hyperventilation associated with pregnancy results from the respiratory stimulating effects of progesterone and leads to hypocarbia ($PaCO_2$ 27–34 mmHg) and a mild respiratory alkalosis (pH of 7.40–7.45).

Labor pain, periodic changes in venous return due to uterine contractions, and maternal expulsive efforts increase CO approximately 45% above prelabor levels. These physiological stresses can be minimized by good analgesia and anesthesia, careful fluid and hemodynamic management, as well as careful positioning to avoid aortocaval compression.[10]

Further increases in preload occur after delivery due to autotransfusion from the contracting uterus and relief of aortocaval compression.[11] These fluid shifts cause further stress on an already potentially compromised cardiac lesion. Postpartum normalization of systemic vascular resistance (SVR) and loss of the low resistance placental bed increases afterload. Careful fluid and hemodynamic monitoring for days to weeks postpartum are essential to minimize potential problems in this crucial period.

Symptoms and signs of normal pregnancy and heart disease

Easy fatigability, dyspnea, and orthopnea of normal pregnancy may simulate heart disease. Orthopnea is more common in obese women and may be due to limitation of diaphragmatic motion. Chest pain during pregnancy is most often due to hiatal hernia, esophageal reflux, or distension of the ribcage. Tachycardia is normal in pregnancy, as are premature atrial and ventricular depolarizations. Orthostatic syncope may occur with sudden assumption of the upright position. Syncope occurring in later pregnancy is usually due to supine hypotension secondary to inferior vena caval compression.

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Table 1.1 Cardiovascular effects of commonly used anesthetic and obstetric drugs

	Heart rate	Blood pressure	SVR	Cardiac output	Myocardial contractility	Venodilation
Etomidate	↔	↔ or ↓	↔ or ↓	↔	↔	↔
Ketamine	↑↑	↑	↑ or ↔	↑	↑[a]	↔
Thiopental	↑	↓↓	↔ to ↑[b]	↓	↓	↑
Propofol	↑ or ↔	↓	↓↓	↔ to ↓	↓	↑
Succinylcholine	↔ to ↓ with repeat doses	↔ to ↑	↔ to ↑	↔	↔	↔ to ↓
Atracurium	↔ or ↑	↔ to ↓	↔	↔	↔	↔ to ↑
Pancuronium	↑	↑	↔ to ↑	↑	↑	↔
Rocuronium	↔ or ↑	↔	↔	↔	↔	↔
Vecuronium	↔	↔	↔	↔	↔	↔
Fentanyl	↓	↔ to ↓	↔	↔	↔	↔
Meperidine	↔ or ↑	↓	↓	↓	↓	↑
Morphine	↔ or ↓	↓	↓	↓	↓	↑
Halothane	↔ or ↑	↓	↓	↔ or ↓	↓↓	↓
Isoflurane	↑↑	↓	↓↓	↔ or ↑	↓	↓
Sevoflurane	↑	↓	↓	↔ or ↓ ?	↓	↔
Nitrous oxide	↔ or ↑	↔ or ↑	↔ or ↑	↓ or ↑	↔	↔ or ↓
Lidocaine	↔	↔	↔	↑	↑	↑ if used for regional anesthesia
Lidocaine toxicity	↓	↓	↑	↓	↓	↑
Midazolam	↔ or ↑	↓	↔ or ↓	↔	↔ or ↓	↔
Ergometrine	↑	↑↑	↑	↑	↑	↓
Oxytocin	↔ or ↑	↔ to ↑ (<10 U) ↓ (>10 U bolus dose)	↔ to ↓	↔	↔	↔ to ↑
Magnesium sulfate	↔ or ↓	↓	↓	↔	↔	↑
Nitroglycerin	↔	↓↓	↔ to ↓	↓	↔	↑↑
Terbutaline	↑	↔ to ↓	↔ to ↓	↑	↔ to ↑	↑

The response is represented by a five-point scale from a marked increase (↑↑) to marked decrease (↓↓), ↔ is no effect, ↑ is a slight increase, ↓ is a slight decrease.

[a] Secondary effect from endogenous catecholamine release

[b] May decrease due to histamine release

There are various caveats in the interpretation of these data. Some values are derived from animal studies, some from human volunteers, and some from patients. Values may vary depending on whether a patient is mechanically ventilated or breathing spontaneously. In addition, the hemodynamic effects of these agents may change in the presence of other anesthetic agents. Finally, the hemodynamic response may be different in patients who are hypovolemic, have sympathetic overactivity, or a sympathectomy. The values and ranges indicated in this table are the authors' opinion of the most likely clinical response for most patients and have been taken in part from the following texts:

Bowdle, T.A., Horita, A. & Kharasch, E.D. (eds). *The Pharmacologic Basis of Anesthesiology: Basic Science and Practical Applications*. New York: Churchill Livingstone, 1994 and Norris, M.C. (ed). *Obstetric Anesthesia*. Philadelphia: J.B. Lippincott, 1993.

Some cardiovascular findings on physical examination may be confusing. Peripheral edema occurs in 60–80% of pregnant individuals, and is attributed to hemodilution, a fall in plasma oncotic pressure, and an increase in capillary pressure secondary to raised venous pressure in the legs. However, this is not associated with hepatomegaly. Rales are likely the result of upward displacement of the diaphragm. Prominent peripheral and neck veins are related to the hypervolemia of pregnancy and the vasodilatory effects of progesterone. However, mean right atrial pressure is not elevated and the hepatojugular reflex is not positive. Pseudo-cardiomegaly is related to displacement of the apex by the gravid uterus. There is often a third heart sound due to volume loading and right ventricular outflow tract murmurs are common.

Certain symptoms and signs suggest the presence of heart disease. A careful history and physical examination will allow these to be differentiated beyond the symptoms and signs of normal pregnancy. Symptoms suggestive of heart disease

Table 1.2 New York Heart Association (NYHA) functional capacity and objective assessment[a]

Functional capacity	Objective assessment
Class I. Patients with cardiac disease but without limitation of physical activity. Ordinary physical activity does not cause fatigue, palpitations, dyspnea, or angina.	*No* objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.	Objective evidence of *minimal* cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina.	Objective evidence of *moderately severe* cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or angina may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of *severe* cardiovascular disease.

[a] AHA medical/scientific statement: 1994 revisions to classifications of functional capacity and objective assessment of patients with diseases of the heart. *Circulation* 1994; **90**: 644.

Table 1.3 Maternal mortality associated with heart disease in pregnancy

Group 1: Mortality <1%	
	Atrial septal defect
	Ventricular septal defect
	Patent ductus arteriosus
	Pulmonary/tricuspid disease
	Tetralogy of Fallot, corrected
	Bioprosthetic valve
	Mitral stenosis, NYHA class I and II
Group 2: Mortality 5–15%	
2A	Mitral stenosis NYHA class III–IV
	Aortic stenosis
	Coarctation of aorta, without valvular involvement
	Uncorrected Tetralogy of Fallot
	Previous myocardial infarction
	Marfan syndrome with normal aorta
2B	Mitral stenosis with atrial fibrillation
	Artificial valve
Group 3: Mortality 25–50%	
	Primary pulmonary hypertension or Eisenmenger syndrome
	Coarctation of aorta, with valvular involvement
	Marfan syndrome with aortic involvement

Adapted from: Foley, M.R.: Cardiac disease. In Dildy, G.A., Belfort, M.A., Saade, G.R., Phelan, J.P., Hankins, G.D. & Clark, S.L. (eds.), *Critical Care Obstetrics*, 4th edn. Malden: Blackwell Science, 2004, pp. 252–74.

include severe or progressive dyspnea, progressive orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, syncope with exertion, and chest pain related to effort or emotion. Physical findings strongly suggesting the presence of heart disease include cyanosis, clubbing, persistent neck-vein distension, palpable murmurs, diastolic murmurs, dysrhythmias, and true cardiomegaly.

Table 1.4 Normal hemodynamic and ventilatory parameters in the nonpregnant and pregnant patient

	Nonpregnant	Pregnant	Percentage change
Cardiac output (l/min)	4.3 ± 0.9	6.2 ± 1.0	+45%
Heart rate (beats/min)	71 ± 10	83 ± 10	+17%
Systemic vascular resistance (dyne.sec.cm^{-5})	1530 ± 520	1210 ± 226	−21%
Pulmonary vascular resistance (dyne.sec.cm^{-5})	119 ± 47	78 ± 22	−34%
Mean arterial pressure (mmHg)	86 ± 8	90 ± 6	NSC
Pulmonary capillary wedge pressure (mmHg)	6.3 ± 2.1	7.5 ± 1.8	NSC
Central venous pressure (mmHg)	3.7 ± 2.6	3.6 ± 2.5	NSC

NSC = no significant change.
Adapted from: Clark, S.L., Cotton, D.B., Lee, W. *et al.* Central hemodynamic assessment of normal term pregnancy. *Am. J. Obstet. Gynecol.* 1989; **161**: 1439–4.

General management principles of pregnant women with heart disease

1. *Take a detailed history and follow up patients regularly during pregnancy*
   Patients with significant heart disease are usually diagnosed prior to pregnancy and may develop worsening of symptoms during their pregnancy. However, some cardiac lesions associated with few symptoms in the nonpregnant state may become symptomatic for the first time in mid to late pregnancy. The hemodynamic changes that occur in pregnancy represent a

significant stress test. Most women with cardiac disease who remain asymptomatic throughout pregnancy usually tolerate labor and delivery. Conversely, women who are breathless at rest (NYHA IV) and groups 2 and 3 listed in Table 1.3, usually tolerate pregnancy poorly. Functional class NYHA III–IV patients with surgically correctable lesions should be assessed for corrective surgery before pregnancy.

2. *Understand the physiological changes of pregnancy*
   It is essential to understand the impact of physiological changes of pregnancy on the specific heart lesion in order to properly manage these patients.[12]
3. *Multidisciplinary team approach*
   Pregnant women with significant or complex heart disease should be managed by a team in a specialist center.[13] This team should include representatives from obstetrics and perinatology, anesthesiology, neonatology, cardiology, intensive care, nursing, and social work. Patients should be seen regularly throughout their pregnancy and a management plan should be formulated early in pregnancy before the onset of labor. High-risk women should be managed by senior anesthesiologists experienced in treating pregnant patients with cardiac lesions. Pediatric involvement is important, as there is a 5–15% chance that the fetus will be affected by the same cardiac defect.[14] In addition, the fetus may be compromised by the mother's cardiopulmonary insufficiency.[15] In-utero echocardiography at 18 weeks' gestation can detect most fetal cardiac defects.[16,17] Avoidance of pregnancy, or consideration of an early therapeutic termination, in women with very high-risk cardiac disease (e.g., pulmonary hypertension) is prudent.
4. *Infective endocarditis antibiotic prophylaxis*
   Although the risk of bacteremia following normal delivery is low (0–5%),[13] appropriate antibiotic coverage should be provided for high-risk patients (especially those with prosthetic valves or a history of endocarditis) prior to labor, delivery, or other surgical procedures (Tables 1.5 and 1.6).[18]
5. *Anticoagulation during pregnancy and peripartum*
   Pregnancy is a hypercoagulable state, which increases the risk of thromboembolic events, especially in the cardiac patient with a prosthetic heart valve, valvular heart disease, or heart failure.[1] Anticoagulant therapy should be considered in these high-risk patients to prevent thromboembolism or thrombus formation.

Warfarin: The use of oral anticoagulants during pregnancy is relatively contraindicated. Warfarin therapy in the first trimester is associated with an increased incidence of fetal death and birth defects ("warfarin embryopathy"). Warfarin use later in pregnancy is associated with prematurity and low birthweight, as well as neonatal cerebral hemorrhage.[19,20] Despite these risks, warfarin is sometimes administered in combination with low dose aspirin (80–100 mg/day) to patients with mechanical valves because of concerns about the efficacy of heparin in preventing systemic embolism.[21,22] Warfarin can be used in the postpartum period and appears safe in women who breast-feed.[23]

Heparin: Heparin, unfractionated (standard, UFH) or low molecular weight (LMWH), is the drug of choice during pregnancy because it is a large molecule that does not cross the placenta and appears safe in women who breast-feed. Heparin is used to prevent and treat thromboembolism. For UFH, the activated partial thromboplastin time (aPTT) should be monitored because heparin requirements increase as pregnancy progresses. Platelet count should be measured before neuraxial blocks in patients on UFH for more than 4 days because of the risk of heparin-induced thrombocytopenia.[24] For LMWH, monitoring of aPTT or anti-Xa level is not predictive of the risk of bleeding and is therefore not always necessary or recommended.[24] Low molecular weight heparin offers potential advantages over UFH including lack of need for laboratory monitoring, greater bioavailability, once-a-day dosing because of its long half-life, and less thrombocytopenia and osteoporosis. Its efficacy in preventing and treating thromboembolism (as well as the above mentioned advantages) are leading to the widespread use of LMWH in obstetrics.

Thrombolytics: Streptokinase and urokinase are relatively contraindicated in pregnancy because of reports of placental abruption and postpartum hemorrhage.[25] Streptokinase has been used successfully to treat prosthetic mitral valve thrombosis during pregnancy.[26] The thrombosis was confirmed by echocardiography and fluoroscopy at 28 weeks' gestation in a woman with a history of progressive exertional dyspnea. Valve function returned to normal within 18 hours of commencing treatment.

Table 1.5 Endocarditis prophylaxis risk stratification

High-risk category (endocarditis prophylaxis recommended)
Prosthetic cardiac valves, including bioprosthetic and homograft valves
Previous bacterial endocarditis
Complex cyanotic congenital heart disease (e.g. single ventricle states, transposition of the great arteries, Tetralogy of Fallot)
Surgically constructed systemic pulmonary shunts or conduits
Moderate-risk category (endocarditis prophylaxis recommended)
Most other congenital cardiac malformations (other than those above and below)
Acquired valve dysfunction (e.g. rheumatic heart disease)
Hypertrophic cardiomyopathy
Mitral valve prolapse with mitral regurgitation ± thickened leaflets
Negligible-risk category (no greater risk than the general population and endocarditis prophylaxis *not* recommended)
Isolated secundum atrial septal defect
Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 months)
Previous coronary artery bypass graft surgery
Mitral valve prolapse without mitral regurgitation
Physiologic, functional, or innocent heart murmurs
Previous Kawasaki disease without valve dysfunction
Previous rheumatic fever without valve dysfunction
Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

From: Dajani, A. S., Taubert, K. A., Wilson, W. *et al.* Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *Circulation* 1997; **96**: 358–66.

Table 1.6 Adult antibiotic prophylaxis for genitourinary/gastrointestinal procedures

Situation[a]	Agents	Regimen[b]
High-risk patients	Ampicillin plus gentamicin	Ampicillin 2.0 g i.m. or i.v. plus gentamicin 1.5 mg/kg (not to exceed 120 mg) within 30 min of starting procedure; 6 h later, ampicillin 1 g i.m./i.v. or amoxicillin 1 g orally
High-risk patients allergic to ampicillin/amoxicillin	Vancomycin plus gentamicin	Vancomycin 1.0 g i.v. over 1–2 h plus gentamicin 1.5 mg/kg i.v./i.m. (not to exceed 120 mg); complete injection/infusion within 30 min of starting procedure
Moderate-risk patients	Amoxicillin or ampicillin	Amoxicillin 2.0 g orally 1 h before procedure, or ampicillin 2.0 g i.m./i.v. within 30 min of starting procedure
Moderate-risk patients allergic to ampicillin/amoxicillin	Vancomycin	Vancomycin 1.0 g i.v. over 1–2 h; complete infusion within 30 min of starting procedure

i.m. = intramuscular; i.v. = intravenous

[a] Endocarditis prophylaxis *not* recommended for routine C/S and prophylaxis is optional for high-risk patients undergoing vaginal delivery.

[b] No second dose of vancomycin or gentamicin is recommended.

From: Dajani, A. S., Taubert, K. A., Wilson, W. *et al.* Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *Circulation* 1997; **96**: 358–66.

Table 1.7 ASRA guidelines for regional anesthesia in the anticoagulated patient[a]

Anticoagulant/thrombolytic	Neuraxial placement considerations	After placement / epidural catheter removal
Low dose LMWH[2] (e.g. enoxaparin 0.5 mg/kg/day, dalteparin 120 U/kg q 12 h)	10–12 hours after the last LMWH dose.	After placement: first dose 6–8 hours; second dose no sooner than 24 hours after the first dose. After removal: minimum of 2 hours.
High dose LMWH[b,c] (e.g. enoxaparin 1 mg/kg q 12 h)	No sooner than 24 hours.	After placement: no sooner than 24 hours. Indwelling catheters should be removed prior to starting LMWH. After removal: minimum of 2 hours.
Heparin IV[d,f]	1 hour before any subsequent heparin administration or 2–4 hours after the last heparin dose.	1 hour.
Prophylactic heparin SC[d,e,f]	None.	None.
Warfarin	Discontinue 4–5 days prior; INR <1.5 before considering regional anesthesia.	Neuraxial catheters should be removed when INR <1.5.
Aspirin and NSAIDs	No special dosing or timing considerations.	No special dosing or timing considerations.
Platelet inhibitors (e.g. ticlopidine, clopidogrel, GP IIb/IIIa)	14 days for ticlopidine. 7 days for clopidogrel. Platelet GP IIb/IIIa inhibitors: eptifibatide and tirofiban (8 h) to abciximab (48 h).	14 days for ticlopidine. 7 days for clopidogrel. Platelet GP IIb/IIIa inhibitors: eptifibatide and tirofiban (8 h) to abciximab (48 h).
Thrombolytics (e.g. streptokinase)	Avoid except in highly unusual circumstances.	Avoid except in highly unusual circumstances.

[a] Adapted from the ASRA 2002 published guidelines: Horlocker, T. T., Wedel, D. J., Benzon, H. *et al.* Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg. Anesth. Pain Med.* 2003; **28**: 172–97.

[b] LMWH therapy should be delayed for 24 hours if the presence of blood during needle and catheter placement occurs.

[c] Higher doses may require more caution.

[d] It may be prudent to confirm that partial thromboplastin time (PTT) is within normal range prior to removal.

[e] The risk of neuraxial bleeding may be reduced by delaying the heparin injection until after the block, and may be increased in debilitated patients or after prolonged therapy.

[f] Due to heparin-induced thrombocytopenia, patients receiving heparin >4 days should have a platelet count prior to neuraxial block.

Anesthetic considerations: Many women with cardiac disease will be treated with anticoagulants to avoid thromboembolism. The decision to perform neuraxial anesthesia in a patient receiving thromboprophylaxis should be made on an individual basis. The American Society of Regional Anesthesiology (ASRA) guidelines should be considered when performing any regional anesthetic on a patient taking anticoagulants (Table 1.7).[24] The patient's coagulation status should be optimized and level of

anticoagulation carefully monitored before spinal or epidural placement and at epidural catheter removal. In patients who have received neuraxial blocks, postprocedure neurological monitoring needs to be carried out at regular intervals (<2 hours between neurologic checks). The epidural infusion should be limited to dilute local anesthetics that minimize sensory and motor block to aid neurological assessment.[24]

6. *Uterotonic agents*
   Care should be exercised when administering oxytocin to patients with cardiac disease since a large bolus can cause hypotension and tachycardia and has been shown to cause increases in cardiac stress.[27] A slow infusion of a dilute oxytocin solution is usually well tolerated. Other uterotonic agents such as ergometrine can induce systemic hypertension and coronary vasoconstriction. Prostaglandin F2-alpha has the potential to cause severe pulmonary hypertension if large doses are injected directly into the circulation.[28]
7. *Peripartum monitoring*
   The level of monitoring, beyond standard American Society of Anesthesiology guidelines, should be appropriate for the severity of the cardiac lesion and the planned obstetric or anesthetic intervention. Invasive monitoring is advised in symptomatic patients with known cardiac defects. Monitoring of radial artery pressure ± central venous pressure (CVP) ± pulmonary artery catheter ± transesophageal echocardiography (TEE) allows precise, continuous measurement of hemodynamic variables and guides appropriate use of fluid and drug therapy. When the pathophysiology of critically ill obstetric patients cannot be explained by noninvasive hemodynamic monitoring and the patient fails to respond to conservative medical management, invasive hemodynamic monitoring may be helpful in guiding further management.[29] The benefits of additional hemodynamic data provided by invasive monitoring should be weighed against the risks associated with invasive line insertion.[30,31]
8. *Basic hemodynamic goals*
   Although care must be individualized to the cardiac lesion and patient condition, basic maintenance of hemodynamic goals are applicable to most cases.
   - Avoid sudden alterations in HR and maintain normal sinus rhythm.
   - Maintain preload and minimize sudden increases or decreases in central blood volume. Pregnant patients with cardiac disease are at increased risk of developing pulmonary edema.
   - Avoid sudden decreases in afterload and SVR. Decreases in SVR are compensated for by increasing HR, which can lead to worsening cardiac function.
9. *Vaginal versus cesarean delivery*
   There are advantages and disadvantages of both vaginal and cesarean section (C/S) with no convincing evidence that either option is clearly superior (Table 1.8).[32] The delivery plan should be individualized according to the woman's condition. Vaginal delivery may be preferable if obstetrically indicated, however, limits to the duration should be discussed and preparations for a potential C/S considered. Assisted delivery is recommended to avoid prolonged pushing, a rapid expulsive phase and Valsalva maneuvers. Although induction of labor in pregnant patients with cardiac disease is safe,[33] there are higher maternal and neonatal complications compared to healthy controls.
10. *The critical postpartum period*
    The immediate postpartum period is critical, especially if pulmonary hypertension is present. Most fatalities occur in the first week after delivery, but others occur as late as three to four weeks postpartum. For this reason invasive monitoring should not be discontinued immediately after delivery, and full therapeutic and monitoring support in a critical care setting should be provided. Postoperative pain management (e.g., epidural analgesia) is useful in reducing the cardiovascular stress response following C/S. In addition, a neuraxial-induced sympathectomy may improve microvascular flow and reduce the risk of perioperative deep vein thrombosis.

Table 1.8 Hemodynamic advantages and disadvantages of vaginal birth and elective cesarean section

	Vaginal birth	Cesarean section
Advantages	Minimize blood loss	Predictable and planned
	Minimize surgical stress	Timed delivery
	Quicker recovery	All personnel immediately available
	Hemodynamic stability	
Disadvantages	Unpredictable timing	Increased surgical stress
	Potentially prolonged	Higher blood loss
	Painful and stressful	Longer recovery
	Potentially "after-hours"	Higher potential postoperative complications

Valvular lesions

Women with stenotic lesions do not tolerate the changes in HR or increases in CO that occur during pregnancy. Any woman with a symptomatic stenotic lesion warrants very close attention and possible correction before or during pregnancy.

Mitral stenosis

Mitral stenosis (MS) accounts for 90% of rheumatic heart disease in pregnancy, with 25% of patients developing symptoms for the first time during late pregnancy. Mitral stenosis is the most common cardiac pathology associated with acute pulmonary edema in pregnancy, followed by aortic valve disease and primary myocardial disease. Symptoms depend on the severity and include fatigue and dyspnea on exertion initially, but may progress to paroxysmal nocturnal dyspnea, orthopnea, and shortness of breath at rest. Mitral stenosis is considered severe when the valve area is 1 cm^2 or less. Overall mortality is around 1% in mild disease or 5–15% in severe mitral valve disease.
Predictors of adverse events include:[7,34,35]

- mitral valve area <1.5 cm^2
- NYHA functional class >II

- left ventricular ejection fraction (LVEF) <40%
- a previous cardiac event.

Pathophysiology

A small mitral valve area causes a decrease in left ventricular (LV) filling and LV output. There is a concomitant increase in left atrial (LA) volume and pressure, with an increased pulmonary capillary wedge pressure (PCWP). These result in irreversible elevation in pulmonary vascular resistance (PVR) over time so that pulmonary edema and pulmonary hypertension can develop. Right ventricular hypertrophy, dilatation, and failure may then occur, causing peripheral edema.

Relative obstruction across the valve increases as pregnancy advances because of the increase in blood volume, HR, and CO. Increased obstruction leads to pulmonary venous congestion and may produce pulmonary edema.

Management principles[36]

- Maintain sinus rhythm and prevent rapid ventricular rates. Atrial fibrillation and tachycardia can also precipitate worsening cardiac function. Aggressively treat new onset atrial fibrillation pharmacologically or with direct cardioversion especially in the hemodynamically compromised patient (see Chapter 2).
- Avoid large, rapid falls in SVR. This is compensated for by increasing HR, which can worsen cardiac function.
- Prevent increases in central blood volume. Careful fluid management and diuresis may be necessary.
- Avoid factors that may increase pulmonary artery pressure (PAP) (see Table 1.9). Prostaglandins, which may be useful in treating uterine atony, can precipitate increases in pulmonary vascular pressure.

Table 1.9 Factors affecting pulmonary vascular resistance (PVR)

Factors decreasing PVR	Factors increasing PVR
↑ PaO_2	Hypoxia
↓ $PaCO_2$	↑ $PaCO_2$
Alkalemia	Acidosis
Medications: phosphodiesterase III inhibitors (e.g. milrinone), prostaglandin E1 and I2, isoprenaline, inhaled nitric oxide	Medications: prostaglandin F2-alpha, nitrous oxide.
Spontaneous ventilation	Positive pressure ventilation and PEEP
	Hypothermia
	Sympathetic stimulation: pain, light anesthesia, anxiety

PEEP = positive end-expiratory pressure

Adapted from: Lovell, A. T. Anaesthetic implications of grown-up congenital heart disease. *Br. J. Anaesth*. 2004; **93**: 129–39.

- The enlarged left atrium promotes thrombus formation and anticoagulation prophylaxis should be used in patients with atrial fibrillation or a prior embolic history.
- Bacterial endocarditis prophylaxis should be administered although its role in an uncomplicated labor and delivery is controversial.
- Beta-blockers may reduce the incidence of pulmonary edema.[37]
- Consider valvuloplasty or valve surgery. Valvuloplasty or valve surgery before pregnancy may reduce the complications during delivery.[38] Patients who develop severe symptoms during early pregnancy may benefit from a second trimester valvuloplasty.[39,40] Intractable heart failure or pulmonary edema are indicators for urgent surgical intervention or balloon valvuloplasty.[41,42] Balloon mitral valvuloplasty should be considered for mitral valve areas <1.5 cm^2 [13] and for refractory pulmonary edema.[43] However, appropriate radiation screening should be provided and plans made in case of sudden valve rupture. Overall percutaneous balloon mitral valvuloplasty carries fewer fetal and maternal risks than open surgical valvotomy and can be performed under local anesthesia with light sedation (e.g., 0.5–1 mg i.v. midazolam).

Anesthetic options

Evidence-based data on the ideal anesthetic and analgesic for the parturient with MS is lacking.[44] Management must be individualized to optimize patient outcome. The degree of monitoring should be based on the severity of the disease and the woman's condition.[44] The concomitant use of invasive hemodynamic monitors is recommended in symptomatic parturients with critical stenosis.[45,46]

It is important to minimize pain and catecholamine release during labor. A carefully titrated epidural for labor and delivery addresses all the above mentioned hemodynamic goals. Epidural analgesia during the first stage of labor can reduce PVR and SVR, lower PAP, and decrease CO to baseline levels.[45] Rapid prehydration should be avoided, and slow titration of local anesthetic solution is recommended to minimize hemodynamic changes. When treating hypotension, phenylephrine is preferred over ephedrine, which may increase the HR. Epinephrine-containing local anesthetic solutions are best avoided due to concerns about potential tachycardia. Combined spinal–epidural (CSE) analgesia may be a good option for these patients.[44,47] An intrathecal opioid combined with a dilute epidural infusion minimizes sympathetic block and concomitant hypotension. Trendelenburg position may help to improve cardiac index and PCWP,[48] but may be uncomfortable for the awake patient. Consider assisted delivery to limit maternal Valsalva maneuvers and expulsive efforts.

Both epidural and general anesthesia (GA) have been described for C/S. Epidural anesthesia has an advantage over a subarachnoid block in that it can be slowly titrated. Epidural anesthesia has been used successfully in women with severe MS undergoing urgent C/S.[48] If GA is required, avoid drugs that produce tachycardia such as atropine, pancuronium, ketamine, and meperidine. Although most anesthetic agents have a negative inotropic effect, (see Table 1.1) patients with mild disease can tolerate a sodium

thiopental induction. Patients with more severe disease may benefit from a "cardiac" anesthetic induction with an intravenous (i.v.) opioid and a cardiostable induction agent (e.g. etomidate). Although opioids (e.g. alfentanil, fentanyl) can provide hemodynamic stability, transplacental drug transfer may cause neonatal respiratory depression.[36] Remifentanil may be the preferred opioid in the peripartum setting due to its short context-sensitive half-life.

The lowest possible dose of uterotonic agent is recommended as it may produce significant adverse cardiovascular effects. The intrapartum and immediate postpartum periods are high risk as the PCWP increases in the presence of severe MS (functional class III and IV).[49] In the appropriate patient, C/S may be followed by immediate corrective surgery, for example closed mitral valvotomy.[50] Postoperative ventilation and intensive care may be necessary. Patients may need inotropic support as well as a pulmonary vasodilator such as nitroglycerin or sodium nitroprusside.

Aortic stenosis

Symptomatic aortic stenosis (AS) is associated with higher neonatal and maternal mortality rates.[51,52] Asymptomatic pregnant patients tolerate pregnancy without complications.[53] Valve area is a better index of severity than gradient estimation, which is often exaggerated in pregnancy due to the high flows.[54] Patients usually become symptomatic (syncope, angina, and dyspnea on exertion) as the valve area decreases to 1 cm^2 and a critical valve area is $<0.6\ cm^2$. A systolic pressure gradient >50 mmHg between the LV and aorta means severe stenosis; however, some patients may not be able to generate large pressure gradients if they have LV dysfunction. Transvalvular gradients increase progressively throughout pregnancy, as a consequence of increased blood volume and reduced SVR. Coexisting coarctation, symptomatic AS at the onset of pregnancy, and cardiac deterioration are considered important risk factors for the woman with AS in pregnancy.[53]

Pathophysiology

A small aortic valve causes increased pressure and work for the LV. Left ventricular hypertrophy results and the thickened myocardial walls are more prone to ischemia. The higher the transvalvular gradient, the greater the risk of myocardial ischemia. These patients have a fixed SV because of the decreased diameter of the aortic valve. Eventually, the LV fails causing a decrease in CO.

Management principles

- Avoid sudden decreases in venous return and LV filling. Decreases in left ventricular end diastolic volume (LVEDV) are poorly tolerated and will cause a decrease in SV and CO in a patient with limited reserve. Augmented preload with i.v. fluids may be of benefit in maintaining a fixed SV. However, pulmonary congestion secondary to LV failure may be exacerbated by fluid loads in the presence of hypervolemia associated with pregnancy.
- Maintain sinus rhythm. Bradycardia is poorly tolerated since these patients have a fixed SV. Patients rely on increases in HR to increase their CO. In addition, the myocardium receives its oxygen supply during diastole and the thickened myocardium is adversely affected by a reduced perfusion time associated with tachycardia.
- Avoid decreases in SVR. A drop in SVR cannot be compensated for by an increase in SV because of the fixed outlet obstruction. Patients with AS increase their HR to maintain CO, but this also increases oxygen consumption and decreases diastolic filling.
- Avoid hypotension. Hypotension causes ischemia in the hypertrophied ventricular muscle. Diastolic BP is important if coronary blood flow is to be maintained.[55]
- Consider valvuloplasty. In some cases, percutaneous balloon aortic valvuloplasty has been performed during pregnancy with good maternal and fetal outcomes.[56] Aortic balloon valvuloplasty in pregnancy may be performed in symptomatic severe AS as a palliative procedure.[57] Valvuloplasty is usually reserved for cases of severe symptomatic AS when aortic valve area is $<1.0\ cm^2$.[13]

Anesthetic options

Some anesthesiologists prefer GA in patients with AS.[55] This is out of concern that sympathectomy from regional anesthesia will reduce SVR and induce tachycardia and hypotension. However, there are a number of case reports advocating carefully titrated epidurals for labor and delivery in parturients with severe AS.[27,53,58] More recently, continuous spinal analgesia and anesthesia have been used successfully for labor and C/S.[59,60] A continuous spinal technique using incremental doses may minimize sympathectomy-induced cardiovascular changes and provide a more controlled hemodynamic profile.[60] When using a regional technique, it is important to slowly titrate the local anesthetic and opioid with invasive monitoring appropriate for the severity of the AS. A single-shot spinal technique is not recommended.[61] Regional anesthesia avoids the tachycardia and stress response from intubation and surgical stimuli associated with GA.

Pain and anxiety can increase SVR and afterload. A slow reduction in SVR with an epidural technique may improve CO in the face of a fixed SV, assuming that the filling pressures are adequate. Some authors recommend avoiding epinephrine-containing epidural local anesthetic solution, while others have used it in the test dose in parturients with cardiac disease.[27] Phenylephrine is the drug of choice to treat hypotension. Unlike ephedrine it improves LV filling without causing tachycardia.[62]

There is no good evidence to show whether regional or GA is safer in patients with AS.[63] If GA is required, an opioid-based anesthetic is useful when LV function is compromised and in cases of severe AS.[55,64] Remifentanil has been used to blunt the hemodynamic response to intubation in patients with AS undergoing C/S under GA.[65] In one report, remifentanil provided cardiovascular stability in conjunction with rapid emergence from anesthesia with minimal neonatal side effects.[65] A standard general anesthetic rapid sequence induction with sodium thiopental and succinyl choline may decrease CO.[63] The use of etomidate as an induction agent may be preferable to avoid myocardial depression from sodium thiopental, and tachycardia associated

with ketamine (see Table 1.1). It must be emphasized that a cautious anesthetic technique is necessary in conjunction with invasive monitoring to guide appropriate therapy in the event of adverse hemodynamic changes.

All uterotonic agents should be used cautiously as they may produce significant cardiovascular effects. Postpartum monitoring is vital as mortality has been reported up to three to five days following delivery.[55]

Regurgitant valvular lesions

Chronic mitral or aortic regurgitation is usually well tolerated during pregnancy if the patient remains asymptomatic or only mildly symptomatic.[66] The physiological changes of pregnancy with reduction in SVR and tachycardia favor forward flow and limit the regurgitant back flow. However, clinical deterioration and heart failure are possible during pregnancy, particularly in patients with LV dysfunction and a reduced ejection fraction.[67]

Mitral regurgitation or insufficiency

Mitral regurgitation (MR) is usually well tolerated and patients can be asymptomatic for many years. Left ventricle dysfunction and heart failure eventually develop if the condition is left untreated. The increased intravascular volume associated with pregnancy and delivery may worsen LV volume overload. Patients are also at risk for atrial fibrillation, pulmonary edema, emboli formation, and endocarditis.

Pathophysiology

Regurgitation of blood from the LV into the LA occurs during systole. This causes LA enlargement with eventual increases in LA pressure. This pressure is transmitted to the pulmonary circulation causing elevations in pulmonary venous pressure and PCWP. This eventually causes pulmonary edema and may lead to RV failure. The LV may also fail secondary to an increase in volume load. Pain and surgical stimulation can increase SVR, which might decrease forward flow across the valve.

Management principles

- Prevent increases in SVR, as an elevated SVR can impair forward flow. Treatment should be aimed at afterload reduction.
- Maintain a normal to slightly elevated HR, avoiding bradycardia. A slow HR prolongs diastole and allows for a longer period of regurgitation. Ephedrine may be a good drug to use in this setting to prevent and treat hypotension and avoid bradycardia associated with alpha-agonists. Treat dysrhythmias aggressively if they occur.

Anesthetic options

Asymptomatic patients probably do not need invasive monitoring, but severely compromised patients should have invasive monitoring to guide fluid and drug therapy. Epidural analgesia is favored for labor pain because it attenuates an increase in SVR from peripheral vasoconstriction secondary to the pain of labor. Reducing SVR increases the forward flow component across the valve.

If patients tolerate the supine position with left uterine tilt, then regional anesthesia is a good choice for C/S. If GA is necessary, try avoiding anesthetic agents with significant myocardial depressant effects (see Table 1.1), especially in patients with LV dysfunction. Techniques that cause a slight increase in HR may be beneficial (e.g. ketamine).

Aortic regurgitation or insufficiency

Most patients with aortic regurgitation (AR) tolerate the cardiovascular demands of pregnancy, although patients with significant LV enlargement and dysfunction may develop heart failure.

Pathophysiology

Left ventricular volume overload causes LV dilatation and increased LV volume, work that eventually leads to LV dysfunction. The regurgitant volume depends upon the diastolic pressure gradient between the aorta and the LV, as well as the duration of diastole. The decrease in SVR seen in pregnancy can improve AR by decreasing the regurgitant volume. However, the increase in intravascular volume associated with pregnancy and uterine contractions can lead to volume overload and LV dysfunction.

Management principles and anesthetic options

The management principles and anesthetic options for AR are the same as for patients with MR (see above).

Mixed valvular lesions

Mixed valvular lesions often present a dilemma as to which lesion to treat and which hemodynamic goals to adopt. As a general rule, therapy should be directed to the management of the dominant, most severe valvular lesion. For example, if a woman presents with severe MR and mild MS then management should be directed to treat the regurgitant lesion, even if this conflicts with the usual treatment of MS.

Management principles

General management goals and monitoring outlined earlier in the chapter should be followed and should be appropriate for the patient's condition. Often a compromise is reached for maintenance of hemodynamic objectives in mixed lesions.[68] Importantly, avoid rapid HR and treat dysrhythmias aggressively. Maintain preload, minimize sudden increases in central blood volume and avoid sudden decreases in SVR. Use cardiovascular monitoring appropriate for the severity of the underlying lesion and the patient's clinical condition.

Anesthetic options

Refer to the anesthetic management options for specific valvular lesions discussed earlier. Treatment must be individualized and no absolute recommendations can be made because evidence-based data are lacking. However, there are a number of case reports describing the successful management of pregnant women with mixed valvular lesions. In one such case report, a woman with moderate to severe MR and mild MS was managed with epidural analgesia for induced labor and ventouse-assisted vaginal delivery.[69] Other reports have described the use of epidural analgesia for labor and delivery in women with combined mitral and aortic regurgitation,[70] and combined MS and AS.[71] More recently, a parturient with mixed pulmonary stenosis and aortic incompetence had a C/S under epidural anesthesia.[68]

Valvulotomy and prosthetic valves

There have been many reports of successful pregnancy following valvular surgery.[72] Generally, women who are asymptomatic before pregnancy are able to tolerate pregnancy and delivery.[67] Symptomatic patients with underlying LV dysfunction and/or pulmonary hypertension may not tolerate the stresses of pregnancy. Compared to pregnant women with prosthetic valves, patients with previous valvotomies have fewer complications and less fetal morbidity.[73] Women with prosthetic valves are at higher risk of complications including valve infection, thromboembolism, and bleeding due to anticoagulant therapy.[74]

Women with aortic valve replacement have a lower incidence of complications than those with a mitral valve prosthesis,[75,76] possibly due to better ventricular function and less stringent anticoagulation compared to mitral valve lesions.[73] All women with prosthetic valves are at risk for valvular infection and clinicians should consider bacterial endocarditis prophylaxis (see Tables 1.5 and 1.6). Anticoagulation should be considered throughout pregnancy due to the high risk of thromboembolism. American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines should be considered,[21] although they were produced before data regarding LMWH for pregnant patients with prosthetic valves were available.[77]

ACC/AHA recommendations[21]

From week 1 to week 36 of pregnancy, high-risk women (thromboembolic history or older generation mechanical mitral valves) should be maintained on warfarin (± low dose aspirin) to keep the INR between 2–3.[21] After week 36, warfarin should be discontinued. However, because of the risk of warfarin embryopathy some women opt to use heparin as an alternative therapy during pregnancy. High-risk patients not taking warfarin should receive continuous UFH keeping aPTT levels around two to three times control.[21,66] Low-risk women can receive subcutaneous heparin. In the absence of bleeding, heparin or warfarin can be restarted four to six hours after delivery.[21] Some institutions use LMWH maintaining peak anti-Xa levels between 0.8 to 1.5 and trough levels at least 0.7.[77] Anti-Xa levels should be checked twice monthly and adjusted as necessary.[77] Patients still on anticoagulants are at risk for postpartum hemorrhage. If regional anesthesia is planned, allow an adequate time between anticoagulation administration and regional (epidural and/or spinal) anesthesia (see Table 1.7).

Regular assessment of signs and symptoms may help detect any residual or new valve dysfunction. It is important to exclude residual myocardial dysfunction or pulmonary hypertension that may exist despite correction of the valvular lesion. Consider invasive monitoring where significant residual myocardial dysfunction or pulmonary hypertension exists. Patients with a valve prosthesis are at higher risk for developing dysrhythmias, especially atrial fibrillation. Management goals and anesthetic considerations should be individualized according to the lesion. (See specific valvular lesions.)

Mitral valve prolapse

Mitral valve prolapse (MVP) is the most common valvular lesion – occurring in approximately 2–4% of the general population – and is most prevalent in young women. A benign course can be expected in 85% of patients with MVP,[78] but 15% develop MR over time. Most patients progress uneventfully during pregnancy and the peripartum period;[79,80] however, some patients may sustain cardiac dysrhythmias (e.g. supraventricular and ventricular tachydysrhythmias, bradydysrhythmias, and conduction blocks). The role of routine endocarditis prophylaxis for labor and delivery is controversial.[79] The current recommendation is that bacterial endocarditis prophylaxis is only necessary in MVP with MR and/or thickened leaflets (see Tables 1.5 and 1.6).

Management principles

Avoid decreases in preload by providing adequate volume replacement and left uterine displacement. Maintain afterload and avoid increases in HR. Hypovolemia, venodilation, increased airway pressure, and tachycardia all decrease LV volume causing an earlier prolapse of the valve leaflets and thus increasing MR. Conditions that increase LV volume, such as bradycardia, afterload augmentation, hypervolemia, or negative inotropic agents, cause later prolapse, with a delayed click.

Asymptomatic patients with MVP require only routine management.[73] Continue antidysrhythmic therapy and make provisions for urgent management of dysrhythmias (see Chapter 2). In patients with MVP and associated symptomatic mitral regurgitation, the hemodynamic goals are similar to those for MR.

Anesthetic options

For pain relief in labor, epidural analgesia is a good choice for patients with MVP and MR. Avoid epinephrine-containing local anesthetics in patients with dysrhythmias.

Regional anesthesia for C/S in parturients with MVP has been reported.[81] Adequate volume loading prior to placement of a regional anesthetic is necessary to avoid LV volume reduction and an increase in MV prolapse. Light GA accompanied by tachycardia

can increase MVP.[73] Drugs that cause tachycardia should be avoided. Shivering and peripheral vasoconstriction can increase LV systolic pressure and increase regurgitant flow. Hence, it is important to maintain normothermia and treat regional anesthesia-induced shivering with i.v. meperidine 12.5–25 mg.

Cardiomyopathy in pregnancy

Currently, nearly 8% of pregnancy-related deaths are caused by cardiomyopathy,[82,83] and this number appears to be increasing. Cardiomyopathy in pregnancy can be divided into peripartum cardiomyopathy and other cardiomyopathy (dilated, hypertrophic obstructive, or restrictive).[82]

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is defined by the National Institutes of Health and is based on four criteria:[13,84,85,86]

- development of cardiac failure in a six-month period (last month of pregnancy to within five months after delivery)
- no identifiable cause
- new diagnosis with no prior heart disease before the last month of pregnancy
- echocardiographic findings of LV dysfunction similar to dilated cardiomyopathy: ejection fraction <45% and a LV end diastolic dimension >2.7 cm/m^2.

Peripartum cardiomyopathy accounts for 70% of the pregnancy-related deaths from cardiomyopathy and is one of the leading causes of maternal death.[82,87] The condition is fatal in 15–50% of cases and the risk of death is higher in black women (six times), women >35 years of age, and in multiple gestation.[82] Fortunately, mortality rates from PPCM appear to have decreased in the past decade, most likely related to advances in medical therapy for heart failure.[88]

In addition to PPCM, there are a number of causes of dilated cardiomyopathy. Possible etiologies include ischemia, alcoholism, toxins, thiamine deficiency, connective tissue diseases, metabolic disorders, neuromuscular dystrophies, and viral or other infections. When no identifiable cause is found, PPCM or idiopathic dilated cardiomyopathy should be considered. Idiopathic dilated cardiomyopathy appears to be a separate syndrome from PPCM.[89,90]

Symptoms and signs of heart failure often develop insidiously and must be distinguished from the normal physiologic changes of pregnancy. Women present with fatigue, dyspnea, orthopnea, palpitations, and hemoptysis. Patients with PPCM often have a raised jugular venous pressure and new regurgitant murmurs with a third heart sound or gallop rhythm. A chest radiograph reveals cardiomegaly and signs of heart failure, while the electrocardiogram (ECG) may show dysrhythmias with nonspecific ST- and T-wave changes. Echocardiography confirms dilated hypokinetic ventricles. Serial echocardiographic studies during pregnancy and the postpartum period to monitor LV function are recommended.[91]

The cause of PPCM is unknown. Hypotheses include myocarditis secondary to a viral or autoimmune response.[84] Postmortem studies show enlarged hearts that are soft, flabby, and dilated with variable endocardial thickening or areas of myocardial necrosis. Endocardial biopsy can be considered in patients without improvement after one to two weeks of maximal medical therapy to help diagnosis and exclude other causes of dilated cardiomyopathy.[84,89] Mortality ranges from 15–50%, with death resulting from cardiac failure, dysrhythmia, or thromboembolism.[87,91] Peripartum cardiomyopathy can be associated with pulmonary hypertension and may result in multiorgan failure.[92] The prognosis is worse if the cardiac size has not returned to normal within six months of delivery.

Management principles

Initial treatment is similar to the management of any form of heart failure.[87,93]

- Reduce and optimize preload with sodium and fluid-intake restriction and diuretics. Loop diuretics appear safe during pregnancy, but spironolactone should be avoided.[93]
- Afterload reduction is the mainstay of medical management. Nifedipine, amlodipine, nitroglycerin, and hydralazine have all been used. Although ACE inhibitors are contraindicated in pregnancy due to fetal renal teratogenicity, they may be considered postpartum and appear safe during breast-feeding.[93,94]
- Any vasodilator may compromise utero-placental blood flow and i.v. vasoactive medication administration requires invasive monitoring.
- Consider inotropic support. Digoxin and, if necessary, dopamine, dobutamine, and milrinone can be considered.[95,96] Beta-blockers have been shown to improve outcome in dilated cardiomyopathy.
- Aggressive use of implantable defibrillators has reduced the risk of sudden death in these patients.[88]
- Anticoagulation: PPCM has a high rate of thromboembolism due to bed rest, hemoconcentration from diuresis, and suboptimal CO.[93] Anticoagulation is important, especially if LVEF is <20%.[87] Echocardiographic evidence of intraventricular thrombi should prompt anticoagulation therapy.[97]
- Immunosuppressive therapy in PPCM is not yet fully understood,[98] but should be considered in patients not responding to conventional medical therapy with myocarditis proven on cardiac biopsy.[84] In one series, 78% of women with PPCM had evidence of myocarditis.[99] Immunosuppressive therapy with oral prednisone and azathioprine for six to eight weeks, led to a resolution of the myocarditis and improved LV function.[99] Recently, i.v. immunoglubulin therapy has been used successfully in PPCM.[100]
- Pentoxyfylline therapy (TNF-alpha production inhibitor) has also been used for PPCM with improvement in the 30 patients treated.[101] Continuous veno-venous hemofiltration has been used successfully to treat severe cardiomyopathy after failure of conventional therapy.[96] There is also an isolated report of a successful treatment of PPCM with daily exchange transfusions.[102]
- Heart transplantation is reserved for severe cases unresponsive to all medical therapy[103] and has been performed successfully

in patients with PPCM.[104,105,106] Intraaortic balloon pump or ventricular assist devices have been used as a bridge to cardiac transplant.[95,104,105,106]

Anesthetic options

If patients can be stabilized on medical therapy, induction of labor is recommended. However, if the woman's condition worsens, C/S should be considered since she may not tolerate a prolonged stressful labor. Consider invasive monitoring appropriate for the patient's condition.[107] Early administration of a labor epidural is important to minimize the stress of labor. Slow titration of the epidural is important. The sympathectomy-induced reduction of afterload following neuraxial anesthesia is potentially beneficial provided BP is maintained.[108] Intrathecal opioids via a CSE or continuous spinal technique are an option for labor analgesia.

If the patient is able to tolerate the supine left-tilt position, an epidural anesthetic for C/S is probably the best option. A continuous spinal anesthetic has been used successfully in a patient with severe PPCM;[109] however, a single-shot spinal technique is not recommended because the subsequent rapid hemodynamic changes may not be well tolerated. Epidural anesthesia with noninvasive hemodynamic monitoring has been reported for C/S.[107]

If GA is necessary, a "cardiac" induction technique with a cardio-stable induction agent (e.g. etomidate) and high doses of opioid are recommended. In one case report, a patient with undiagnosed cardiomyopathy suffered a cardiac arrest at induction of GA for emergency C/S.[110] Fortunately, the mother and baby were successfully resuscitated.

There is no consensus on the possibility of subsequent pregnancies in survivors of PPCM.[13,84] In patients not recovering ventricular function and in heart failure, future pregnancies are not recommended. Even in women who have recovered clinically, 20% will deteriorate in subsequent pregnancies. In a woman with previous PPCM and normal ventricular function at rest, systolic dysfunction can be unmasked using dobutamine echocardiography.[111] Failure to tolerate this stress test may indicate that the patient will not be able to tolerate a future pregnancy. Echocardiographic evidence of LV dysfunction includes fractional shortening <20% and LV end diastolic dimension >6 cm.[112] Recurrence of PPCM is possible and mortality associated with a recurrence is even higher.[113]

Hypertrophic obstructive cardiomyopathy

Hypertrophic obstructive cardiomyopathy (HOCM) or idiopathic hypertrophic subvalvular stenosis (IHSS) is a disease that is characterized by a dynamic LV outflow tract obstruction, caused by a contracting hypertrophied ventricle and septum during systole. This disease usually affects patients in their 20s to 30s and is occasionally seen in pregnancy. Most patients have a fairly benign course, but patients with HOCM are at increased risk for dysrhythmias and sudden death. Affected patients may be asymptomatic or have mild symptoms (palpitations, dyspnea on exertion, angina, and syncope). Some patients with HOCM may deteriorate and progress to congestive heart failure. Clinically, patients have signs of LV hypertrophy with a late systolic murmur at the apex.

Hypertrophic obstructive cardiomyopathy is a disease transmitted by autosomal dominant inheritance with variable penetration. Asymmetrical septal and LV hypertrophy are hallmarks of this disease, causing a *dynamic* outflow tract obstruction during systole. Obstruction to LV outflow is caused by a hypertrophic muscle mass at the base of the interventricular septum. There is an apical obliterative variety, which does not have a subaortic pressure gradient. However, in most cases, a subaortic pressure gradient is present and the ventricle is less compliant. This leads to a reduction in passive ventricular filling during diastole. Atrial contraction becomes an important factor in increasing LVEDV.

Factors that impact on the degree of obstruction include LVEDV, force of ventricular contraction, and transmural pressure that distends the outflow tract. Inotropic agents or conditions that increase myocardial contractility and SVR will worsen the outflow obstruction. Conditions that decrease preload will also worsen obstruction by decreasing LV volume. When the LV outflow tract is narrowed, CO falls and MR may occur since the mitral valve becomes the point of relief for the build up of ventricular pressure.

In pregnancy, the decrease in SVR along with an increase in HR and contractility are physiologically deleterious to this condition. Conversely, an increase in intravascular volume allows for a larger ventricular volume and decreases outflow obstruction. A decrease in preload associated with aortocaval compression in the third trimester and the Valsalva maneuver during delivery can increase outflow obstruction. Usually, the physiological changes of pregnancy are well tolerated in patients with HOCM.[114] However, latent HOCM may become a clinical problem and sudden death from HOCM has been reported in pregnancy.[115,116]

Management principles

- Where appropriate, use invasive monitoring in symptomatic patients or patients with atrial dysrhythmias.
- Avoid decreases in preload. Increased blood volume and maintenance of venous return is important in order to minimize outflow obstruction.
- Maintain a normal to slow HR and aggressively treat any atrial dysrhythmias. Tachycardia limits diastolic filling, which decreases LVEDV and increases contractility, which, in turn, will increase LV outflow tract obstruction.
- Avoid increases in contractility as this increases the dynamic obstruction and may reduce CO. Beta-blockade is useful in patients with HOCM to treat LV outflow obstruction by reducing cardiac contractility and HR. However, there is concern that beta-blocker therapy during pregnancy might cause fetal bradycardia and intrauterine growth restriction (IUGR). The use of esmolol is controversial and there have been reports of hypotonia, hypotension, hypoglycemia, and bradycardia in a neonate born to a parturient with HOCM treated with esmolol.[115,117]

Labetalol in 0.25 mg/kg increments up to 1 mg/kg may be preferable.
- Avoid sudden decreases in SVR. Maintenance of SVR will decrease outflow obstruction.
- Treat hypotension with an alpha-agonist (e.g. phenylephrine or metaraminol). Try to avoid ephedrine as it may increase the dynamic obstruction.

Anesthetic options

Vaginal delivery is considered safe, although attempts should be made to minimize the period of "bearing down" during the second stage of labor. Regional anesthesia has been used successfully in laboring patients with HOCM despite concerns about associated afterload reduction.[115,118] Appropriate prehydration, monitoring, and the use of drugs like phenylephrine or metaraminol to maintain SVR are important. Both conventional epidural[119] and CSE[120] have been used in this setting to provide labor analgesia. In one case report, continuous spinal analgesia with an opioid as the sole intrathecal agent provided excellent pain relief and hemodynamic stability.[118] The intrathecal opioid allowed rapid analgesic onset without the sympathetic block and afterload reduction.[118,120] Epidural and continuous spinal analgesia attenuate increases in HR and contractility from endogenous catecholamines (pain and anxiety) during labor. Expulsive efforts and Valsalva maneuvers can be reduced by effective epidural analgesia. Ephedrine is contraindicated in the treatment of hypotension associated with HOCM due to the risk of tachycardia, therefore phenylephrine (50 μg increments) is the treatment of choice for hypotension following sympathetic blockade. Ropivacaine has theoretical advantages over bupivacaine in that it is less cardiotoxic. However, low concentrations of bupivacaine can be used safely in these patients.

Spinal and epidural anesthesia for C/S cause a reduction in preload and afterload, which has a potential adverse impact in patients with HOCM.[119,121] The successful use of GA for C/S has been described in women with HOCM.[122] Although volatile anesthetic agents are beneficial in that they produce a reduction in myocardial contractility they should be used cautiously to avoid a marked fall in SVR. While GA is traditionally recommended for these patients, carefully titrated epidural anesthesia has been used successfully for C/S.[123] A single-shot spinal anesthetic is not recommended because of the rapid onset of sympathetic blockade. Subarachnoid anesthesia for an orthopedic procedure in a patient with HOCM resulted in an increased left ventriculo-aortic gradient, and concomitant deterioration in coronary perfusion.[121]

The critical determinants of a good outcome are careful titration of anesthetic agents, adequate volume loading, and prompt replacement of blood loss guided by invasive hemodynamic monitoring. Although the tachycardia and hypotension associated with oxytocin are problematic in women with HOCM, a dilute oxytocin infusion will likely be well tolerated.[122] Postpartum pulmonary edema in parturients with IHSS has been reported.[124] Patients should be closely monitored for worsening outflow obstruction resulting from the diuresis that occurs in the first 48–72 hours postpartum.

Heart transplant recipients (see Chapter 22)

Aortic dissection

There is an association between pregnancy and aortic dissection, and 50% of all dissections in women under 40 years old occur during pregnancy.[125,126] Maternal mortality is very high, but is similar to the nonpregnant state. Although aortic dissection is rare, it is an important cause of maternal mortality.[3,4,66] Possible etiological factors of aortic dissection during pregnancy include connective tissue disease (in particular, Marfan syndrome), severe preeclampsia, sepsis, atherosclerosis, and coarctation of the aorta (see Chapter 3). The diagnosis should be suspected in anyone with abdominal, thoracic, or interscapular pain; however, painless dissection is common with Marfan syndrome. There is cardiovascular involvement in 80% of patients with Marfan syndrome.[3] Presentation depends on the extent and location of the dissection with 70% affecting the ascending aorta.[73] Diagnosis is made by computed tomography (CT) scan or TEE.

Management principles

Nonemergent situation: The decision to repair the aorta should be based on the patient's condition and gestational age of the fetus. The risk of dissection increases with the duration of pregnancy and the diameter of the ascending aorta. In a case series of pregnant women with acute aortic dissection, most dissections happened in the third trimester.[127] The ascending aorta at time of dissection was 4.8 cm. *Aortic diameters over 4 cm are generally considered critical.* Monthly ultrasound inspections of the aorta are recommended to detect possible early rupture. Premature delivery via C/S or induction of labor is recommended when the aortic root diameter is greater than 4.5 cm.[13,127] Management should be individualized and based on a multidisciplinary team reviewing the patient's condition throughout pregnancy. Before fetal viability, aortic repair with a fetus *in situ* is justified given the high mortality of nonoperative treatment.[128,129] If the fetus is viable, primary C/S or vaginal delivery with concomitant or staged surgical repair is indicated.[125]

Emergent situation: In the case of acute rupture or hemodynamic deterioration, expedited surgery and resuscitation may be necessary. Cesarean section should be performed once control of the aortic dissection is achieved.

Anesthetic options

Regional anesthesia is recommended for labor pain as it can effectively reduce sheer wall stress and wall tension associated with pain during labor and delivery.[66] Vaginal delivery under regional anesthesia has been described in patients with Marfan syndrome and aortic dissection.[130] The BP should be kept normal or slightly below normal. All antihypertensive medication should be continued peripartum. Beta-blockers can be titrated to control the BP during labor and delivery.[66] Preparations should be made

for possible rupture with large-bore i.v. access, blood and resuscitation equipment available.

The best anesthetic method for C/S is controversial. General anesthesia is associated with a hypertensive response to intubation and surgical stimulation that may promote rupture or dissection progress. Efforts should be made to prevent increases in BP and to reduce the cardiovascular response to endotracheal intubation. General anesthesia may be necessary in the anticoagulated patient or in the emergent situation. In Marfan syndrome, regional anesthesia can be associated with marked hypotension and increased risk of epidural hematoma due to epidural vein fragility.

Cardiopulmonary bypass during pregnancy

The first extracorporeal circulation or cardiopulmonary bypass (CPB) during pregnancy to facilitate open-heart surgery was described by Leyse *et al.*[131] in a woman at 18 weeks' gestation with congenital AS. Cardiopulmonary bypass has been necessary during pregnancy and in the peripartum period to facilitate open-valve surgery and to manage individual cases of aortic dissection, massive pulmonary embolus, amniotic fluid embolus, and coronary artery dissection. If possible, surgery requiring CPB should be delayed until the second trimester, or later. If the parturient tolerates pregnancy, a primary C/S with concomitant or staged CPB with surgical repair can be performed.[132]

Most cardiac operations with CPB during pregnancy can be performed with reasonable safety in the mother, but there is increased risk for the fetus.[133,134] The well-being of the mother and fetus must be considered although the best interests of the two may not always coincide and optimal therapy may be a compromise.[135]

During CPB in pregnancy, high pump flows (30–50% increase over the nonpregnant state) should be maintained. Perfusion pressures >60 mmHg appear optimal to maintain utero-placental perfusion.[1] One report describes the successful treatment of fetal bradycardia during CPB by increasing the perfusion rate.[136] Hypothermia can reduce utero-placental perfusion and cause fetal hypoxia.[3] Temperatures <32°C have the potential to cause fetal dysrhythmias and cardiac arrest. Continuous intraoperative fetal monitoring is important during CPB in order to detect fetal dysrhythmias and bradycardia.

Another problem associated with CPB during pregnancy is severe postpartum hemorrhage. This was described during an emergency mitral valve replacement immediately after C/S.[137] Aprotinin, a protease inhibitor, has been used to effectively treat a similar problem in an obstetric patient following CPB.[138] Patients requiring CPB should be managed in a tertiary center with multidisciplinary team involvement.[135]

Peripartum ischemic heart disease

Acute myocardial infarction (MI) in pregnancy is relatively rare with a reported incidence of 1 in 10 000.[139] However, the incidence can be expected to increase due to advancing maternal age, tobacco, and cocaine abuse.[1,140] Peripartum MI carries substantial maternal and fetal morbidity and mortality.[140,141] Overall maternal and fetal mortality ranges from 21–37% and 12–34% respectively.[140,141] Maternal mortality is greatest (approximately 45%) if the MI is late in pregnancy, or when delivery occurs within 14 days of the initial infarction.[140,141]

Pathophysiology

Myocardial ischemia occurs when oxygen demand outstrips oxygen supply. In MI during pregnancy, atherosclerosis is found to be the cause in less than half the cases.[140] The coronary arteries often appear normal at angiography[140,142] and other suggested causes include coronary spasm, arteritis (e.g. Kawasaki Disease – Chapter 3), or *in situ* thrombosis.

Normal pregnancy is accompanied by increases in HR, myocardial wall tension, basal metabolic rate, and oxygen consumption. Labor and delivery lead to further increases in oxygen consumption and demand, which may seriously compromise women with ischemic heart disease (IHD). The increase in oxygen consumption peaks at the time of delivery, and remains elevated in the immediate postpartum period. Even asymptomatic patients with coronary artery disease during pregnancy are at risk of ischemia or infarction during the peripartum and postpartum periods.

Most cases of peripartum MI are in patients without a history of IHD. Characteristic symptoms, ECG changes and serial elevated cardiac enzymes diagnostic of MI in nonpregnant patients, are less reliable during pregnancy.[66] Signs and symptoms of myocardial ischemia in pregnancy can be similar to normal signs and symptoms of pregnancy. These include poor exercise tolerance, shortness of breath, diaphoresis, and chest pain. In normal pregnancy the ECG may show left-axis deviation and reversible ST-, T-, and Q-wave changes. ST-segment depression is common during C/S under regional anesthesia without evidence of myocardial ischemia.[143] If an MI during pregnancy is suspected, diagnosis can be confirmed by measuring cardiac specific troponin I levels >0.15 ng/ml. Creatine kinase levels may not be helpful since they increase during normal labor.[144]

An exercise stress ECG or echocardiography with inducible ischemia helps to confirm the diagnosis of IHD. Recommendations for stress testing during pregnancy should follow the ACC and the AHA guidelines.[145] Heavy exercise during pregnancy may decrease uterine blood flow, and testing should be done with fetal monitoring and an exercise goal limited to 70% maximum HR.[146] Echocardiography is safe in pregnancy; however, the safety of pharmacologic stress-testing echocardiography is unknown.

Management principles

- Efforts should be made to *limit myocardial oxygen demand and maximize supply* throughout pregnancy and during parturition. Myocardial ischemia occurs when oxygen demand outstrips oxygen supply.
- Anemia should be treated and hematocrit maintained above 30%.
- Medical management of IHD includes optimal positioning to avoid aortocaval compression, oxygen administration, aspirin,

beta-blockers, nitroglycerin infusion, calcium channel blockers, and anticoagulation. Aspirin is considered safe at doses <150 mg per day, especially during the second and third trimester.[22] Although there are no reports of teratogenicity with beta-blockers, there have been reports of intrauterine growth restriction (IUGR), fetal bradycardia, hypoglycemia, and hyperbilirubinemia at birth with both propranolol and esmolol therapy. Selective beta-blockers are probably safer with fewer fetal complications reported. Nitroglycerin infusion and calcium channel blockers may have tocolytic effects and therefore may increase the risk of uterine atony. Angiotensin-converting enzyme inhibitors and statins are contraindicated in pregnancy and should be avoided.

- There are a number of successful reports of percutaneous coronary angioplasty following MI in pregnancy.[147,148,149] However, there are no reports of this revascularization option in pregnant patients with stable coronary artery disease.
- Successful coronary artery bypass grafting during pregnancy has been reported.[150] Although the risk of CPB during pregnancy is similar to that of nonpregnant patients (3% overall), the fetal mortality remains high at 19%.[150]
- Thrombolytic agent (e.g. streptokinase, tissue plasminogen activator) administration to pregnant women has been reported in the literature.[140,151,152] However, the potential risks of maternal and fetal hemorrhage may outweigh the benefits.
- Although experience is limited, percutaneous coronary angioplasty ± stenting may be the treatment of choice in pregnant patients with MI.

Anesthetic options

Patients should be managed in a setting where continuous ECG monitoring can occur. If possible, delivery should be postponed at least two weeks after an MI.[140,153] Cautious use of oxytocin is important to avoid hypotension.[154] Ergot alkaloids (e.g. methergine) may cause coronary spasm and should be avoided.[3] Prostaglandin F2-alpha (hemabate) should also be used with caution as it may cause hypertension in the systemic and pulmonary circulations.

It is important to provide optimal pain relief during labor in order to minimize the cardiovascular stress of labor and delivery. This can be achieved by a slow controlled induction of epidural analgesia. If patients are anticoagulated, follow ASRA guidelines (see Table 1.7) prior to inducing a neuraxial block. There are advantages and disadvantages of vaginal and C/S with no convincing evidence that either option is superior[32] (see Table 1.8). Some authors prefer vaginal delivery if obstetrically indicated.[141] However, limits to the duration of labor should be discussed and preparations for a potential C/S considered. The use of forceps or vacuum to assist delivery and minimize prolonged pushing is preferable.

A regional anesthetic technique is appropriate for C/S provided preload is maintained and reflex tachycardia is avoided. Afterload reduction associated with regional anesthesia is beneficial in decreasing cardiac demand. Slowly titrated epidural anesthesia is ideal to prevent abrupt fluctuations in preload and afterload. A single-shot spinal technique is relatively contraindicated. Consider light sedation (e.g. midazolam i.v. 0.5–1 mg) to minimize anxiety and pain during line and epidural placement. Shivering increases oxygen consumption and must be treated aggressively (e.g. meperidine i.v. 12.5–25 mg). Avoid shivering by using fluid warmers, forced air warmers, and increasing the operating room temperature. Phenylephrine is the drug of choice to treat hypotension and minimize an increase in HR. Preventing an increase in HR is critical because tachycardia increases myocardial demand and reduces oxygen supply (shorter diastolic coronary perfusion time). If GA is necessary for obstetric indications, then a high dose opioid technique is recommended to reduce the cardiovascular response to endotracheal intubation and surgery.

Continuous postpartum monitoring is essential. Patients should be managed by a multidisciplinary team for optimal outcome. Specialist advice is necessary if these patients are contemplating future pregnancies, and future cardiac risk will depend upon post-MI cardiac function.[155]

Congenital heart disease in the pregnant patient

General principles

In developed countries, pregnant women with CHD outnumber those with rheumatic heart disease.[13,156] With improvements in surgical and medical management, an increasing number of patients with corrected or partially corrected CHD are surviving to childbearing age and presenting for labor and delivery. The outcome of a pregnant woman with CHD is related to her NYHA functional status, the type of lesion, and the nature of prior palliative or corrective surgery. In particular, patients with severe LV outflow tract obstruction, pulmonary hypertension, or cyanotic heart disease are at greater risk from pregnancy.[13]

The anesthetic management of obstetric patients with CHD is challenging and there is a lack of evidence-based literature to guide management due to the rarity and heterogeneity of lesions. Furthermore, the anesthetic approach toward two parturients with the same CHD lesion may differ significantly depending on the severity of the lesion (i.e. minimal end-organ cardiopulmonary effect versus end-stage Eisenmenger syndrome (ES) versus postpalliation versus postcomplete repair).[157,158] Regardless of the CHD lesion, the strategy should be to identify the cardiopulmonary pathophysiology (primary and secondary), and manage it within the context of the physiologic changes of pregnancy. Any parturient with a significant CHD lesion should be managed in conjunction with a cardiologist at a tertiary care facility.[157,159] As the infant is also at risk of CHD (2–16%),[160] these infants may require specialized care.[77,158]

Patients with CHD lesions should receive bacterial endocarditis prophylaxis ± thromboprophylaxis (see Tables 1.5 and 1.6). Meticulous care is required in patients with CHD shunt lesions to ensure all peripheral and central i.v. lines are free of air bubbles.

Monitoring

Patients with CHD require special considerations when planning monitoring needs.[161] Arterial lines may need to be placed on the opposite side of the previous shunt (e.g. Blalock-Tausig shunt).

Central venous cannulae can pose a potential thromboembolic risk in patients with a Fontan type circulation, and pulmonary artery catheterization may be riskier and measurements misleading with significant cardiac lesions and the presence of a shunt.[161] Transesophageal echocardiography is a useful real-time assessment tool for preload, ventricular function, and intracardiac shunt assessment.

Congenital heart disease shunt lesions

Traditionally, CHD shunt lesions have been characterized as either acyanotic or cyanotic (see Table 1.10). This differentiation attempts to classify shunt lesions according to excessive pulmonary blood flow (left-to-right shunt), or inadequate pulmonary blood flow (right-to-left shunt). Many diseases that start as acyanotic lesions may progress to cyanotic lesions as they approach an end-stage. The dynamic nature and complexities of the lesions, as well as the consequences of surgical repairs, further complicate the classification of CHD. (see Table 1.10). Generally, pregnant women with congenital shunt lesions have favorable outcomes provided they have minimal functional impairment and good myocardial function.[162]

Atrial septal defects

There are five different subtypes of atrial septal defect (ASD). These include patent foramen ovale (PFO), secundum ASD (80% of ASD), primum ASD, sinus venosus ASD with partial anomalous pulmonary venous return (PAPVR), and unroofed coronary sinus.

Table 1.10 Classification of congenital heart disease

Acyanotic shunt lesions	Atrial septal defects[a]
Left-to-right shunts	Ventricular septal defects[a]
	Patent ductus arterioses (PDA)[a]
Cyanotic shunt lesions	Tetralogy of Fallot (TOF)
Right-to-left shunts	Ebstein's anomaly
	Post bidirectional Glenn or preFontan procedure
	Post fenestrated Fontan procedure with elevated pulmonary artery pressure
	Truncus arteriosus
	Total anomalous pulmonary venous return
	Tricuspid atresia
	Hypoplastic left heart syndrome
	D-transposition of the great arteries
Nonshunt lesions	Coarctation of the aorta
	Valvular heart lesions
	Cardiomyopathies
	Fully corrected shunt lesions (ASD, VSD, PDA, TOF)
	Post nonfenestrated Fontan procedure
	L-transposition of the great arteries

[a] NonEisenmenger

- PFO results from intact primum and intact secundum septal fusion failure, and remains patent or probe-patent in an estimated 30% of adults.[163,164]
- Secundum ASD represents an omission of a portion of the septum secundum and is typically located at the midportion of the interatrial septum.
- Primum ASD represents an omission of a portion of the septum primum and is also associated with a cleft anterior mitral valve leaflet with resultant mitral valve regurgitation. Primum ASD increases risk for LV dilatation and systolic dysfunction, LA enlargement, atrial fibrillation, pulmonary hypertension, and RV dysfunction.
- Sinus venosus ASD represents an omission of the portion of the septum secundum proximal to the superior vena cava (SVC). It causes PAPVR into the right atrium (RA) instead of the LA.
- Unroofed coronary sinus ASD represents an absence of a partition between the LA and the coronary sinus. This leads to oxygenated LA blood communicating with deoxygenated RA blood via the coronary sinus conduit.

Isolated ASD lesions originate as predominately left-to-right shunts. The amount of interatrial flow is dependent on the defect size, the relative RA to LA pressure gradient, the presence or absence of atrial contraction, and relative LV and RV compliances during diastole when the atrioventricular valves are open. Chronic atrial level shunting results in RA and RV volume overload with subsequent RA enlargement and atrial dysrhythmias, as well as RV dilatation and RV systolic dysfunction. The pulmonary overcirculation will eventually culminate in pulmonary hypertension, RV hypertrophy, and both RV diastolic and systolic dysfunction. Ultimately, Eisenmenger syndrome can develop as defined by reversal of shunt flow direction (due to fixed pulmonary vascular obstructive changes). Progressive hypoxemia, polycythemia, and right-sided heart failure (jugular venous distension, liver congestion, ascites, protein-losing enteropathies) may eventually develop.

Management principles

The management of the parturient with ASD depends upon the underlying lesion and its clinical consequences. In the absence of clinical evidence of RV dysfunction or pulmonary hypertension, ASD is well tolerated during pregnancy.[162,165] If there is cyanosis, RV dysfunction, or pulmonary hypertension, then invasive monitors and real-time echocardiographic monitoring may be required. Removal of air from all venous lines is essential in order to avoid systemic air emboli (particularly coronary and cerebral emboli).

Hemodynamic goals:

- *Maintain RA contraction*. Normal sinus rhythm preservation is critical, especially in the setting of RV diastolic dysfunction from pulmonary hypertension-induced RV hypertrophy. Both atrial fibrillation and flutter lead to loss of normal atrial contribution to ventricular preload. Rapid atrioventricular conduction will further exacerbate the deleterious effects of these dysrhythmias by causing insufficient ventricular filling time. Antidysrhythmic agents or direct-current synchronized

cardioversion should be considered in this patient population, only after LA thrombosis formation has been ruled out by echocardiography. Antidysrhythmics and rate-controlling medications may be required (e.g. amiodarone, calcium channel blockade, beta-blockade, digoxin). Prior to their administration, cardiologists and obstetric care providers should be consulted so that any adverse effects on the parturient and fetus (e.g. thyroid dysfunction from amiodarone) can be monitored (see Chapter 2).

- *Maintain high to normal heart rates*. This augments RV CO in the setting of impaired RV preload (diastolic dysfunction) and RV SV (systolic dysfunction). High to normal heart rates are essential in the setting of primum ASD where the added chronotropy will help reduce the overall mitral valve regurgitation fraction by reducing mitral valve annular diastolic distention.
- *Maintain RV preload*. A dilated RV with tricuspid regurgitation will require a large RV preload to ensure an adequate SV is available to maintain adequate forward CO and to compensate for the regurgitant back flow. In addition, the restraining effects of a noncompliant RV will cause a fixed upper-limit preload on the RV. Ensuring the RV is maximally filled during diastole is important; otherwise SV, and hence overall pulmonary CO, will be impaired. Proper positioning to avoid aortocaval compression and anticipation of blood loss during delivery will help to maximize RV preload.
- *Contractility* will need to be augmented in patients with RV systolic dysfunction in order to maintain pulmonary blood flow (PBF). This intervention is particularly important in the primum ASD parturient where concomitant LV systolic dysfunction may coexist. Patients with primum ASD will also benefit from the systolically augmented RV pushing more blood through the pulmonary circuit to the dilated LV. Adequate LV preload is necessary to offset the fractional loss of forward SV to the backward mitral regurgitation jet during systole.
- *Prevent increases in pulmonary vascular resistance (PVR)* (see Table 1.9).
- *Maintain SVR* to allow adequate right coronary artery perfusion pressure to the hypertrophied RV.

Anesthetic options

For parturients with ASD undergoing a trial of labor, it is important to provide good analgesia and to minimize the cardiovascular stress of labor and delivery.[1] Epidural (continuous or patient controlled), CSE, or continuous spinal analgesia (CSA) are all acceptable neuraxial analgesic techniques. However, if the patient exhibits any coexisting coagulation abnormalities or is taking anticoagulants, then neuraxial regional anesthesia should be approached with appropriate caution according to established guidelines (see Table 1.7). Neuraxial anesthetic techniques, type of analgesics, dosages, and combination of agents should all be selected with consideration of their therapeutic benefit (pain reduction, positive hemodynamic goal attainment) versus potential deleterious side effects (e.g. hypotension).

Techniques that provide effective analgesia with minimal, slow-onset hemodynamic changes are ideal. Neuraxial local anesthetics will cause a sympathetically mediated decrease in SVR and hence a relative hypovolemia. Obstetric anesthesiologists need to anticipate any accompanying loss of SVR with appropriate volume replacement and the judicious use of vasoconstrictors. To minimize hemodynamic disturbances, slow titration of epidural or intrathecal medication is preferable to a single-shot spinal technique. For maintenance of labor analgesia, a continuous infusion of the lowest possible concentration of local anesthetic is preferable, avoiding, if possible, a large intermittent bolus administration. Saline should be used to determine loss of resistance when locating the epidural space, so as to avoid accidental i.v. injection of air and paradoxical systemic air embolism. Neuraxial opioids have minimal hemodynamic side effects compared to local anesthetics. They can augment the analgesic effects of neuraxial local anesthetics, therefore allowing the use of lower concentrations of local anesthetic with less potential for vasodilation and hypotension. Assisted vaginal delivery to minimize the cardiovascular stress associated with delivery is useful. Analgesic augmentation may be necessary to facilitate assisted delivery.

Since regional anesthesia for C/S has advantages for the mother and fetus, GA is reserved for parturients who require C/S but have contraindications to neuraxial techniques (e.g. coagulopathies, emergency C/S, patients who have severe orthopnea, or patients in cardiopulmonary extremis). Patients with RV failure may have edematous laryngeal tissue due to poor central venous drainage, and this may predispose to difficult intubation conditions. Other drawbacks to GA include loss of endogenous catecholamine balance, which may unmask a failing ventricle and positive-pressure ventilation induced loss of venous return. Advantages of GA include (1) the ability to manipulate oxygenation, ventilation, and anesthetic depth, which are central to the management of patients with severe pulmonary hypertension; (2) the ability to administer the inhaled pulmonary vasodilator nitric oxide; and (3) the ability to use TEE for immediate assessment of cardiopulmonary function.

The choice between regional and GA should be individualized and based on the clinical impact of the ASD. The anesthetic technique should allow the anesthesiologist the best chance of controlling hemodynamic parameters. The risk/benefit ratio of any anesthetic technique must involve an understanding of the pathophysiology of the cardiac lesion.[166]

Ventricular septal defects

Ventricular septal defects (VSDs) are the most common structural heart defect, (approximately 20–35% of all CHD lesions).[161,163,166] There are four major anatomical subtypes of VSD (see Table 1.11). These include perimembranous (PM), muscular, outlet supracristal subarterial (SCSA), and inlet atrioventricular (AV) canal (see Table 1.11). A VSD is often part of a more complex cardiac anomaly (e.g. Tetralogy of Fallot).

Management principles

The management of a parturient with a VSD is very similar to that of a patient with ASD with two major exceptions. Firstly, patients

Table 1.11 Classification of ventricular septal defects (VSD)

VSD subtype	Incidence	Description
Perimembranous	Most common subtype (80% of VSD)	Located in the membranous portion of the interventricular septum (IVS), which stretches between the conal-trigone and muscular septa.
Muscular	10% of VSD	Situated within the muscular-trabecular region of the IVS. Often consists of multiple holes ("Swiss-cheese-like" in appearance).
Supracristal subarterial	4% of VSD	Located distal to the crystal supraventricularis and proximal to the semilunar valves. Usually associated with aortic valve insufficiency as the right ± noncoronary aortic valve leaflets tend to prolapse via a VSD-generated Venturi jetstream effect during diastole.
Inlet atrioventricular canal	6% of VSD	Located in the posterior IVS juxta-tricuspid valve area. Often associated with complete AV canal defects.

with unrestricted shunt flow (i.e. no pressure gradient between the LV and the RV) are predisposed to both accelerated congestive heart failure (CHF) and pulmonary hypertension from the pulmonic overcirculation. Secondly, left-to-right VSD shunt flow can be attenuated by SVR reduction, unlike left-to-right ASD shunt flow, which is uncoupled to SVR.

Anesthetic options

Neuraxial or GA can be used provided the onset of analgesia or anesthetic is initiated in a slow, controlled manner with appropriate hemodynamic monitoring. (See various anesthetic options described under ASD.)

Patent ductus arteriosus

Patent ductus arteriosus (PDA) represents 8–15% of CHD lesions.[161] Patent ductus arteriosus consists of a retained vascular communication between the left pulmonary artery and the proximal descending thoracic aorta distal to the left subclavian artery. A large PDA mimics an unrestricted VSD in that it can lead to pulmonic overcirculation with resultant CHF and pulmonary hypertension. As pulmonary hypertension develops, the left-to-right shunting will diminish and ultimately reverse, resulting in Eisenmenger syndrome.

Management principles (see Atrial septal defects)

The focus of hemodynamic management is to assess the severity of the lesion and to determine the degree of secondary pathophysiology. If the parturient has a small PDA with no signs or symptoms of pulmonary hypertension, RV failure, or hypoxemia, then labor or C/S will likely be uneventful. If, however, there is associated pulmonary hypertension, RV failure, or hypoxemia, then RV inotropic support (e.g. epinephrine, dopamine, milrinone, dobutamine), PVR reduction, SVR maintenance and normovolemia are required. Maintenance of SVR and volume status are also important.

Anesthetic options

The choice between various neuraxial techniques for labor, and between regional versus GA for C/S, should be based on patient condition and the desired hemodynamic goals. (See various anesthetic options described under ASD.)

Cyanotic congenital heart lesions

Congenital heart disease with right-to-left shunt is associated with recirculation of poorly saturated blood. Peripheral cyanosis occurs when >5 g/dl of unsaturated hemoglobin is present. Cyanosis varies directly with hematocrit. It is important to remember that an anemic parturient with poor oxygen saturation may not manifest cyanosis, whereas with polycythemia, cyanosis appears at higher oxygen saturations.[167] Cyanotic lesions are more likely associated with congestive heart failure, worsening of functional status, fetal loss, preterm labor, and IUGR.[15] Fetal, not maternal factors are usually responsible for intolerance of the pregnancy and labor.[168]

A physiologic response to hypoxemia in women with cyanotic lesions is polycythemia, which is a useful compensation up to a hematocrit of 60%. An increase in blood viscosity beyond this level offsets any advantages that an increase in hematocrit brings in terms of oxygen delivery. Symptoms of hyperviscosity include headache, sluggish mentation, disorientation, double-vision, fatigue, muscle weakness, myalgias, and paresthesias.[169] Polycythemia contributes to tissue ischemia in low flow states because of the increase in blood viscosity and can lead to thrombosis *in situ*. Maternal hematocrit >60%, SaO_2 <80%, RV hypertension, and syncopal episodes are all poor prognostic signs in pregnant women with CHD.[170] Cyanotic CHD may be associated with multiple coagulation factor deficiencies increasing the risk of peripartum bleeding.[161]

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common cyanotic CHD lesion and accounts for 5–15% of CHD.[73] Parturients with TOF have an increased risk of adverse events including ventricular failure, dysrhythmias, embolic phenomena, increased fetal loss, and congenital fetal abnormalities.[171] Tetralogy of Fallot consists of (1) nonrestrictive VSD; (2) over-riding aorta; (3) dynamic subpulmonic right ventricular outflow tract (RVOT) obstruction; and (4) RV hypertrophy. The worse the RVOT obstruction, the greater the right-to-left shunt of blood through the VSD.

Other possible secondary pathologies include RV systolic and diastolic dysfunction, and end-organ visceral damage from chronic hypoxemia, polycythemic microvascular sludging and reduced CO. Most parturients with TOF have undergone surgical correction or palliation during childhood. Pregnancy-induced cardiovascular changes can unmask residual symptoms of surgically corrected TOF. Patients with fully corrected TOF usually tolerate pregnancy well; however, dysrhythmias, thromboembolic events, and progressive failure may complicate pregnancy.[171]

If the parturient has a history of corrective surgery during infancy or childhood, then severe pulmonic insufficiency may arise secondary to trans-pulmonic valve annular patching. Right ventricular dilatation, RV systolic failure, and elevated RA pressures may subsequently develop. Ventricular septal defect patch or oversew leaks should be ruled out by echocardiography and by checking baseline room air oxygen saturation.

Management principles

Hemodynamic goals for uncorrected TOF include:

- Maintain normal sinus rhythm to augment RV diastolic filling.
- Maintain adequate RV preload to relieve the dynamic RVOT obstruction.
- Reduce chronotropy to minimize RVOT muscular infundibular spasm.
- Avoid increases in inotropy (e.g. catecholamine surges during labor), which may worsen the dynamic RVOT obstruction.
- Maintain SVR to keep the VSD shunt going left-to-right and to augment right coronary artery perfusion to the hypertrophied RV.

If the parturient with TOF is post transpulmonic valve annular patch repair with residual severe pulmonic insufficiency, then it is important to:

(1) Maintain RV preload to compensate for the RV dilatation. Augment preload with i.v. fluids and avoid sudden decreases in preload following neuraxial or GA.
(2) Maintain RV inotropy if RV systolic dysfunction is present with appropriate inotropes (e.g. epinephrine, dopamine, milrinone, dobutamine).
(3) Maintain RV chronotropy to decrease the diastolic run-off of pulmonary artery blood into the RV through the incompetent or absent pulmonic valve. Heart rates can be maintained with inotropes or anticholinergics as indicated.
(4) Decrease PVR to reduce regurgitant pulmonary artery blood flow back into the lower resistant RV during diastole (see Table 1.9).

Anesthetic options

Various anesthetic and analgesic techniques have been used in patients with TOF for vaginal birth and C/S.[172] The choice between various neuraxial techniques for labor, and between regional versus GA for C/S, should be based on the patient's condition and the desired hemodynamic goals (see Atrial septal defects).

Ebstein anomaly

Ebstein anomaly represents less than 1% of all CHD defects. Although quite variable in its presentation, the basic pathophysiologic features of Ebstein anomaly include:

(1) A downward displacement of both posterior and septal tricuspid valve leaflets into the RV such that the basal portion of the RV becomes "atrialized". This leads to diminished RV cavity size and results in decreased right ventricular stroke volume and CO.
(2) A redundant anterior tricuspid valve leaflet that can cause an obstruction to blood flow through the right side of the heart.
(3) Tricuspid valve regurgitation with concomitant elevated RA pressures and RV systolic dysfunction.
(4) A PFO or secundum ASD with right-to-left shunting due to the high RA pressures.
(5) An increased incidence of supraventricular reentry tachydysrhythmias.

Management principles

The management of a parturient with Ebstein anomaly centers on the severity of the dysrhythmias and right heart failure. Reentry atrial tachydysrhythmias can be managed either medically or by radiofrequency ablation techniques. Right ventricular systolic dysfunction may require exogenous inotropic support, especially as CO requirements increase during pregnancy and delivery. Heart rates should be kept elevated to both minimize tricuspid regurgitation and to maintain pulmonary arterial flow, since RV stroke volume is already impaired. Pulmonary vascular resistance reduction will help minimize regurgitation across the tricuspid valve and promote forward pulmonary CO.

Anesthetic options

General and regional anesthesia have been used successfully in patients with Ebstein anomaly for labor and C/S.[173,174,175] The choice between various neuraxial techniques for labor, and between regional versus GA for C/S, should be based on the patient's condition and the desired hemodynamic goals (see Atrial septal defects).

Coarctation of the aorta

Aortic coarctation comprises approximately 6–8% of the CHD population. Most coarctations are located distal to the left subclavian artery and juxta-opposite the remnant ductus arteriosus tissue (ligamentum arteriosum). Patients with an uncorrected coarctation who reach adulthood generally develop collateral blood flow through nonductal arteriosus mechanisms to allow for viable postcoarctation distal aortic perfusion. Clinically, patients with aortic coarctation exhibit proximal hypertension, distal hypotension, systolic ejection murmurs, LV hypertrophy, and LV diastolic dysfunction. Pregnancy-related changes (decreased SVR, increased blood volume, and increased CO) are poorly tolerated by patients with a coarctation. They are also at increased risk of ascending aortic arch complications (dilatation, aneurysm, and rupture) and premature coronary

artery disease. Coexisting congenitally malformed bicuspid aortic valves may predispose these patients to accelerated AS.

Management principles

Management of parturients with coarctation of the aorta is similar to that of fixed supravalvular aortic stenosis (see Aortic stenosis). The only caveat is that proximal BP (brain, heart) must be measured in the right upper extremity while distal BP (uteroplacental, mesenteric) should be measured in the lower extremity. In addition, proximal hypertension secondary to a coarctation can masquerade as preeclampsia, therefore separate upper and lower extremity BP measurements can help differentiate the two conditions. Preeclampsia in a parturient with a coarctation would be a unique situation that requires aggressive treatment of the proximal hypertension. Although rare, the major maternal risk from a coarctation is aortic dissection, so BP should be aggressively managed.[6] The treatment of upper-limb BP may lead to excessive hypotension below the aorta, causing uteroplacental insufficiency and fetal compromise.[8]

Anesthetic options

Anesthetic choices and considerations are similar to those for patients with aortic stenosis (see Aortic stenosis). Epidural, CSE, and spinal block for labor analgesia and C/S have been used successfully in parturients with coarctation of the aorta.[176,177,178] Single-shot spinal anesthesia is a poor choice due to the potential for precipitous cardiovascular changes.[172] If GA is undertaken, BP increases during endotracheal intubation and surgical stimulation should be minimized (see Aortic stenosis).

Other congenital heart disease lesions

There are many CHD lesions beyond the scope of this chapter. Brickner *et al.* have described various rare CHD lesions.[179,180] Many lesions are incompatible with life or longevity. Some lesions are very rare and therefore are unlikely to present during pregnancy.

There are a number of reports of patients with transposition of the great vessels during pregnancy. Neuraxial and GA have been successfully performed for labor and C/S.[181,182,183] Pregnancy is usually well tolerated in the asymptomatic patient with corrected transposition of the great vessels.[184]

Truncus arteriosus is a rare congenital malformation with a poor prognosis if left untreated. It occurs when only one artery arises from the heart to give rise to the systemic, pulmonary, and coronary arteries. Pregnant patients will usually have surgically corrected lesions and survival to the reproductive years is seen. Management and anesthetic options for C/S have been described in women with truncus arteriosus.[185,186]

The management of pregnant women presenting with complex congenital heart lesions must be individualized. Both general and regional anesthetic options have been used to manage pregnant patients with complex congenital heart lesions in the obstetric setting.[187,188,189,190]

Patients with congenital valvular lesions (e.g. pulmonary stenosis and AS) may present during pregnancy. The management and anesthetic options of congenital valvular lesions are similar to those of aquired valvular lesions (see Valvular lesions). Percutaneous balloon valvuloplasty is the option of choice in patients with severe symptomatic pulmonary valvular stenosis during pregnancy.[13] Labor and C/S in patients with pulmonary stenosis have been successfully managed with epidural, CSE, and continuous spinal anesthesia.[68,187,191]

Due to the rarity and heterogenicity of many adult CHD lesions, good evidence-based literature to guide management and anesthetic options is lacking. While case reports present useful information, they may be limited in their applicability to other patients with a similar lesion. Slight differences between reported cases can have significant hemodynamic consequences. Management guidelines from experts and consensus panels may be valuable sources of information to help plan the management of patients with adult CHD.[159] The desired hemodynamic goals, the choice between regional versus GA for C/S, and analgesic options for labor pain, must be individualized and should be based on the woman's specific lesion and pathophysiology.

Surgically corrected congenital heart disease

Most significant CHD lesions, or lesions that are not compatible with longevity, are usually surgically repaired before pregnancy. Asymptomatic patients with repaired CHD usually tolerate pregnancy and delivery without complications. However, patients with repaired CHD may have residual defects and underlying myocardial dysfunction. Delayed repair of CHD is more likely to be associated with residual ventricular dysfunction. Successful surgical repair of cyanotic CHD lesions prior to pregnancy results in a significant improvement in maternal and neonatal outcomes.[192]

There are many palliative and corrective surgical procedures for CHD (see Table 1.12). Each corrected CHD lesion must be individualized and its current pathophysiological function, as well as the original anatomical lesion, should be considered when planning patient management. Case reports provide interesting, but patient-specific, management plans. Guidelines produced by the European Society of Cardiology may help guide the management of surgically repaired CHD lesions.[159]

Fontan repair

The Fontan procedure is synonymous with total caval-pulmonary arterial direct continuity. The procedure is usually the final stage in a multisurgical approach to correct certain CHD lesions (tricuspid atresia, hypoplastic left heart syndrome, double inlet ventricle, and pulmonary atresia). All post-Fontan patients are considered univentricular, meaning they have been converted to single ventricular physiology, which is solely responsible for supporting systemic CO. This ventricle can be either a morphologic RV or a morphologic LV. If the systemic ventricle is a morphologic RV (as is the case with hypoplastic left heart syndrome), then one needs to have a heightened expectation of encountering

Table 1.12 Common surgical procedures for congenital heart disease

Procedure	Description	Result
Modified Blalock-Taussig	Brachiocephalic artery to pulmonary artery anastomosis; palliative procedure	Increases pulmonary blood flow
Fontan	Anastomosis or conduit between IVC and pulmonary artery; palliative procedure	Increases pulmonary blood flow
Bidirectional Glenn	SVC to pulmonary artery anastomosis; palliative procedure	Increases pulmonary blood flow
Atrial switch	Transection and reimplantation of aorta and pulmonary artery onto the correct ventricles; corrective procedure	Creates normal relationship between the ventricles and the great vessels in transposition
Mustard	Arterial switch with intra-arterial pericardial baffle; corrective procedure	Reestablishes correct flow sequence to pulmonary artery and aorta in D-transposition
Rastelli	Valved conduit from RV to pulmonary artery; corrective procedure	Increases pulmonary blood flow
Ross	Pulmonary autograph to aorta; corrective procedure	Correction of aortic stenosis
Senning	Atrial switch with atrial wall baffle; corrective procedure	Reestablishes correct flow sequence to pulmonary artery and aorta in transposition

Adapted from Segar, D. S. Common surgical procedures for congenital heart disease. *ACC Current Journal Review* 1996; **5**: 46.

morphologic RV systolic failure as the patient reaches adulthood or is exposed to the increased CO demands of pregnancy. A morphologic RV is not designed to pump chronically against SVR and will begin to fail over the years or under physiologic high-output states (e.g. exercise or pregnancy).

The hallmarks of management post-fontan repair are the maintenance of univentricular systolic function and the abatement of pulmonary arterial pressure elevation. Since pulmonary CO is passively driven by the gradient between the CVP and PAP, it is necessary to keep PVR as low as possible. Factors that contribute to PAP elevation (see Table 1.9) warrant close attention. Embolic material entering the pulmonary arterial tree could significantly impede pulmonary blood flow since there is no ventricular pump to force blood past the obstruction. A small subset of post-Fontan patients will have a "fenestrated" modification, which means that an intentional potential right-to-left "pop-off" hole has been created to decompress high central venous pressures. The "pop-off" effect will preserve systemic CO and minimize the adverse effects of caval congestion at the expense of oxygen desaturation.

Pregnancy post-Fontan operation is usually well tolerated although there is a 2% risk of death.[193] Favorable anesthetic management of pregnant women who have previously undergone Fontan repairs has been reported.[194,195] Successful management of a patient with Fontan physiology mandates a thorough understanding of the hemodynamic consequences of this procedure and the alterations during pregnancy.[196]

Pulmonary hypertension and Eisenmenger syndrome

Pulmonary hypertension is defined as a mean PAP >25 mmHg at rest (>30 mmHg during exercise and pregnancy). Pulmonary hypertension secondary to cardiac disease may result from longstanding high pulmonary blood flow due to systemic-to-pulmonary shunts, venous hypertension from cardiac or valvular dysfunction, or chronic thromboembolic disease. Overall maternal mortality is very high (approximately 30–50%) and has not improved significantly over the years despite improvements in medical care and multidisciplinary management.[197]

Symptoms of pulmonary hypertension are nonspecific and often difficult to differentiate from normal pregnancy symptoms. The most frequent symptom is progressive dyspnea in addition to fatigue, chest pain, peripheral edema, and syncope.[198] Cardiac catheterization is the gold standard for assessment of pulmonary hypertension. Echocardiography provides good information of the underlying cardiac defect, myocardial function, and PAP. However, echocardiography may overestimate PAP in pregnant patients with suspected pulmonary hypertension.[199]

Eisenmenger syndrome

This is the final end-stage condition where bidirectional or right-to-left shunting between the systemic and pulmonary circulations occurs as a result of increased pulmonary pressures that approach systemic pressures. Eisenmenger syndrome (ES) may develop in longstanding CHD lesions with large left-to-right shunts and high pulmonary blood flow (e.g. large ASD, VSD, PDA, or large surgical systemic-pulmonary anastomoses following palliation or definitive repairs of CHD). The pulmonary hypertension is secondary to structural changes in the pulmonary vasculature that eventually results in shunt reversal when PAP finally exceeds systemic pressure.

The maternal mortality in patients with ES is very high, ranging from 23–40%.[200,201,202] Women with pulmonary hypertension or ES should not become pregnant and therapeutic terminations should be offered if patients present early in their gestation.

Management principles

- *Monitoring*: Continuous ECG and pulse oximetery with invasive arterial monitoring should always be used.[197] Pulmonary

artery catheterization is controversial and the risk of the procedure should be balanced with the benefit of the additional hemodynamic data that will be obtained.

- It is crucial to maintain the delicate balance between systemic and pulmonary pressures to avoid worsening right-to-left shunting. Maintain SVR and avoid maneuvers that increase PVR (see Table 1.9).
- Consider agents to improve pulmonary hypertension, for example inhaled nitric oxide and inhaled or i.v. prostaglandins (e.g. esoprostenol, iloprost). Intravenous esoprostenol has been used successfully to manage a woman with ASD and ES in late pregnancy.[203] Inhaled nitric oxide transiently improved oxygenation and PAP in a woman with ES in labor and postpartum.[204] L-arginine and sildenafil have been used to treat a woman with severe pulmonary hypertension and ES during pregnancy, delivery, and postpartum with significant improvement in the mother's condition.[205] Chronic medications (e.g. calcium channel blockers) that the patient receives for pulmonary hypertension and cardiac function should be continued.
- Maximize RV function by maintaining appropriate preload and minimizing PVR increases (see Table 1.9). Increases in RV pressure may worsen tricuspid regurgitation and cause the interventricular septum to shift to the left, resulting in a reduction in LV function and CO.
- Provide adequate oxygenation during labor, delivery, and postpartum. This may reduce hypoxic pulmonary vasoconstriction and improve PAP. Oxygen may not improve saturation if significant right-to-left shunting exists.
- Avoid sedatives that may decrease respiratory drive, increase $PaCO_2$, and therefore increase PVR (see Table 1.9).
- Patients are at higher risk for thromboembolic events compared to healthy parturients.
- Use air filters if there is significant right-to-left shunting. However, air filters increase i.v. line resistance and reduce the ability to resuscitate the patient in the case of peripartum hemorrhage.
- Vasoactive agents with predominantly chronotropic and inotropic effects (e.g. ephedrine) or low doses of alpha-agonists (phenylephrine) are preferable when treating hypotension, since high doses of alpha-agonists may increase PVR.
- Uterotonic agents: hypotension and decreases in SVR may occur with bolus administration of oxytocin. An infusion of the lowest possible dose necessary to maintain uterine tone should be used to minimize these cardiovascular effects. Oxytocin has been used for induction of labor without adverse cardiovascular disturbances. Prostaglandin F2-alpha can increase PVR and is relatively contraindicated.[66] Similarly, methylergonovine should be used cautiously in these patients as it also has the potential to produce severe systemic hypertension.

Anesthetic options

Successful use of epidural analgesia has been reported for labor and delivery analgesia[206] and good analgesia is important to minimize cardiovascular disturbances. Opioids should be added to minimize local anesthetic concentrations. A routine test dose should be omitted because of potential epinephrine-induced tachycardia. In patients undergoing a trial of labor, an assisted delivery will minimize expulsive efforts.

The choice between a vaginal birth and C/S will depend on the patient, obstetric, and institutional factors (see Table 1.8). Cesarean section has been associated with higher mortality in patients with ES;[200] however, this statistic may reflect C/S in patients with cardiac decompensation. Traditionally, GA has been used in patients with pulmonary hypertension ± ES. A review of the literature by Martin *et al.*[207] reveals that the surgical procedure and disease, rather than the anesthetic technique, had the greatest impact on outcome. There is no evidence to suggest any anesthetic technique is superior for C/S; however, a trend towards a lower mortality rate is associated with regional anesthesia.[207] There are a number of reports describing the successful use of epidural anesthesia for C/S.[208,209,210] Continuous spinal anesthesia has also been used for C/S in a woman with ES.[211] The stated advantages of this technique are titratable anesthesia, less chance of failed or incomplete anesthesia, and less local anesthetic use. A single-shot spinal technique is not recommended because of the critical importance of maintaining SVR and CO.

General anesthesia has a number of disadvantages, for example, induction agents with myocardial depressive effects (see Table 1.1), and positive pressure ventilation, which may decrease venous return and increase ventilation/perfusion mismatch. Potential advantages of GA include facilitating the use of intraoperative TEE, and administration of inhaled or nebulized pulmonary vasodilators. Transesophageal echocardiography is valuable for patients at risk from hemodynamic disturbance. Transthoracic echocardiography can be of value in monitoring awake patients with regional anesthesia.[212]

A "cardiac" anesthetic utilizing induction agent with minimal negative inotropic and SVR effects (e.g. etomidate) and an opioid-based technique to reduce intubation and surgical response is preferable. Neonatal respiratory depression must be anticipated if high doses of opioids are used. Clinicians should be aware that a slow cardiac induction of GA may lead to pulmonary aspiration. Nitrous oxide can increase PVR and should be avoided if possible. Contraction of the uterus and relief of inferior vena cava (IVC) obstruction immediately following delivery can result in hypervolemia and cardiac decompensation. Careful use of vasodilators with continuous monitoring may be useful at this time. Cardiac decompensation and death are most likely to occur during the postpartum period.[207] Patients should receive several days of intensive care and remain in hospital for at least one to two weeks postpartum.[213]

Summary

Obstetric anesthesiologists should not be dogmatic about the choice of anesthetic for parturients with heart disease. Due to the variation and rarity of cardiac diseases in pregnancy there is no good evidence based on randomized controlled studies to guide our practice. An understanding of the hemodynamic changes associated with pregnancy and the functional impairment of the structural cardiac lesion in question is most

important in providing optimal conditions for labor and delivery. Treatment options must be individualized and based on the patient's hemodynamic condition and obstetric needs.

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2 DISORDERS OF CARDIAC CONDUCTION

Jean E. Swenerton, Ravishankar Agaram, and Victor F. Huckell

Introduction

Disorders of cardiac conduction seen in pregnancy are those involving abnormal impulse generation or propagation (supraventricular, ventricular dysrhythmias, heart blocks) and specific conduction disorders (preexcitation syndromes, long QT syndrome). The clinical implications and current management of some familiar disorders of conduction during pregnancy are discussed but there is an emphasis on the more uncommon disorders of cardiac conduction.

Physiologic heart rate and rhythm changes in pregnancy (see Table 2.1)

In conjunction with the antepartum rise in blood volume, resting heart rate (HR) increases steadily by 10–15% throughout pregnancy, reaching a peak of 10 to 20 beats above baseline during the third trimester. During labor and delivery, sinus tachycardia is seen, with maximal HR occurring peripartum.[1] Parturients with more labor pain may have higher sympathetic tone and higher peripartum HR.

Electrocardiogram (EKG) changes during pregnancy include shift of QRS axis in any direction, the appearance of small q waves in Lead III, T wave inversion and, commonly, ST-T changes. ST segment depression, coinciding with maximal HR and usually asymptomatic, has been reported during nonoperative and operative deliveries. ST changes may result from tachycardia, hormonal milieu, heart position changes, venous air emboli, hypokalemia, and hyperventilation.[2] It is unclear whether the sympathectomy produced by regional anesthesia affects the ECG but both ST segment depression (>1 mm) and ST elevation have been reported during cesarean section (C/S).[2] The clinical significance of ST changes remains uncertain. An uncomplicated nonQ wave anterolateral myocardial infarction (MI) was reported in a primigravida receiving ritodrine and nifedipine for preterm labor at 28 weeks' gestation.[3] Coronary angiography was normal two days later and she had an uncomplicated spontaneous vaginal delivery at 40 weeks' gestation.

Dysrhythmias during pregnancy

There may be an increased propensity for tachydysrhythmias (mainly supraventricular) during pregnancy.[4,5] As the circulation becomes more hyperdynamic some women become more aware of the heart beat, changes in HR, and skipped beats. Proposed mechanisms for pregnancy-induced dysrhythmias include changes in cardiac ion channel conduction, increase in cardiac size (atrial stretch, increased end-diastolic volume), changes in autonomic tone, and hormonal fluxes.[6,7] Cardiac dysrhythmias are more common in parturients with structural cardiac defects (e.g. atrial (ASD) and ventricular septal defects (VSD)), or with abnormal conduction pathways. These dysrhythmias may occur for the first time or be exacerbated by the cardiovascular changes of pregnancy. Long QT syndrome (LQTS), more common in young women compared to the general population, may be associated with ventricular dysrhythmias. Right ventricular (RV) outflow tract dysrhythmias[7] and supraventricular tachycardias (SVT) with reentry are more common in women,[8,9] and may occur during pregnancy. Other causes of cardiac dysrhythmias during pregnancy include electrolyte imbalance (hypokalemia, hyperkalemia), drug interactions (anesthetic drugs, antidysrhythmic drugs, cocaine), and hypo- or hyperthyroidism.

Premature ectopic atrial and ventricular depolarizations (PAD, PVD) and sinus tachycardia are the most common dysrhythmias during pregnancy. Premature atrial beats, generally benign and well tolerated, occur in approximately 50% of women.

Palpitations, dizziness or light-headedness, dyspnea, presyncope and syncope, and chest pain are presenting complaints of a cardiac dysrhythmia (in descending order of frequency). Shotan *et al.*[5] compared the incidence of dysrhythmias in 110 pregnant women without structural heart disease who had palpitations, dizziness, or syncope with 54 pregnant women with an asymptomatic functional precordial murmur. Both groups had a high incidence of dysrhythmias on Holter monitoring (PAD in 56% of symptomatic women vs. 58% of asymptomatic women). Simple and multifocal PVD were higher in symptomatic women. There was no correlation between symptoms and the incidence of dysrhythmias (only 10% of symptomatic episodes had a dysrhythmia). Six weeks' postpartum, there was significant decrease in the incidence of dysrhythmia in nine parturients with documented multiple premature beats,[5] consistent with reports of an increased propensity for tachydysrhythmias during pregnancy. Although dyspnea severe enough to limit activity and syncope with exertion may be normal during pregnancy, these symptoms warrant careful evaluation.

During labor and delivery, nearly all parturients have some form of dysrhythmia[10] (see Table 2.2), which usually has no hemodynamic consequences and rarely requires treatment. Hemodynamically significant dysrhythmias are uncommon and life-threatening dysrhythmias during pregnancy and labor are rare.

As the fetus is vulnerable to the effects of maternal dysrhythmias and their treatment, fetal well-being is a vital consideration in the decision to treat a dysrhythmia and in the choice of treatment.

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Table 2.1 Physiological cardiovascular changes of pregnancy

Cardiac output	Begins early pregnancy
	↑ 2nd and 3rd trimesters
	Interindividual variability[a]
	Further ↑ during labor and delivery[b]
Heart rate	↑ steadily through pregnancy
	Peak 10–20 bpm above baseline 3rd trimester
	↑ with pain and stress
Rhythm	PAD and PVD common
ECG	Shift of QRS axis in any direction
	Small rightward deviation of average mean QRS axis (1st trimester)
	Small leftward deviation due to progressive elevation of left hemidiaphragm (3rd trimester)
	Lead III: small Q-T wave inversion
	Transient ST-T changes common

[a] See text
[b] Depends on physiological changes, blood loss, stress of delivery
PAD = premature atrial depolarizations; PVD = premature ventricular depolarizations; bpm = beats per minute

Table 2.2 Dysrhythmias recorded during labor among 30 women[8]

	no. (%)
Sinus node dysfunction	
tachycardia	30 (100)
bradycardia	15 (50)
Supraventricular dysrhythmia	
isolated PAD	27 (90)
nonconducted P waves	4 (13)
ectopic atrial tachycardia	3 (10)
wandering atrial pacemaker	2 (7)
sinus pause	1 (3)
retrograde P waves	1 (3)
AV junctional dysrhythmia	
accelerated idioventricular rhythm	1 (3)
Ventricular dysrhythmia	
isolated PVD	15 (50)
multifocal PVD	5 (17)
couplet	2 (7)
aberrant intraventricular block	3 (10)
AV block	
first degree	1 (3)
second degree, type I	1 (3)

PAD = premature atrial depolarizations; PVD = premature ventricular depolarizations; AV = atrioventricular

Diagnosis and management of dysrhythmias

A parturient may present with a *new acute dysrhythmia* during labor where urgent diagnosis and treatment is required, or with a *preexisting dysrhythmia* on established drug therapy. In both cases, knowledge of the dysrhythmia, antidysrhythmic drugs, and other methods used to treat dysrhythmias is needed to formulate a safe anesthetic plan. A cardiologist should be consulted as early as possible; however, this is not always possible.

In the acute situation, assess the woman while supporting her airway and breathing, administering oxygen, obtaining a 12-lead ECG to identify the rhythm, and monitoring blood pressure (BP) and oxygen saturation. In general, dysrhythmias in parturients can be assessed by asking the following questions:

- Is the woman hemodynamically stable?
- Is fetal well-being compromised?
- Are there any causative or potentiating factors?
- Is the dysrhythmia likely to progress into a more dangerous dysrhythmia?
- Is treatment required immediately?
- Is treatment appropriate in pregnancy and will it affect the fetus?

General principles of management (see Figure 2.1)

1. When there is no identifiable precipitating factor, no underlying heart disease, and no hemodynamic compromise, reassurance may be appropriate.
2. Successful management may require identification and elimination of precipitating factors only.
3. Clinically significant dysrhythmias requiring treatment most often occur in those who have *underlying structural heart disease* and/or a history of *preexisting dysrhythmia*. In the absence of clinically overt cardiac disease, the dysrhythmia may be the initial manifestation of a congenital or acquired structural heart abnormality (see Chapter 1).
4. Identification and evaluation of underlying heart disease and choice of appropriate treatment are critical for a normal maternal and fetal outcome.
5. If there is hemodynamic compromise, a sustained dysrhythmia, or one predisposing to a ventricular dysrhythmia, immediate synchronized cardioversion is indicated. Serious signs and symptoms are uncommon if the ventricular rate is < 150 bpm (beats per minute) in women with healthy hearts. If impaired cardiac function or significant comorbid conditions are present, symptoms may occur at lower HRs. Definitive and prophylactic treatment in the form of drug therapy, cardioversion, or pacemaker therapy (temporary or permanent) is required while monitoring the mother and fetus. Oxygen and left uterine displacement should be ensured.
6. Diagnosing and treating serious dysrhythmias promptly and appropriately minimizes the risk of embolic events.
7. Avoid myocardial ischemia and electrolyte imbalance in women susceptible to dysrhythmias.

Cardiac assessment of conduction disorders during pregnancy

Cardiology consultation[11] is requested frequently when a pregnant woman has palpitations of uncertain etiology or significance, or a specific conduction disorder.

Noninvasive diagnostic investigations (ECG, Holter event monitor, echocardiogram) are preferred over radiographic studies,

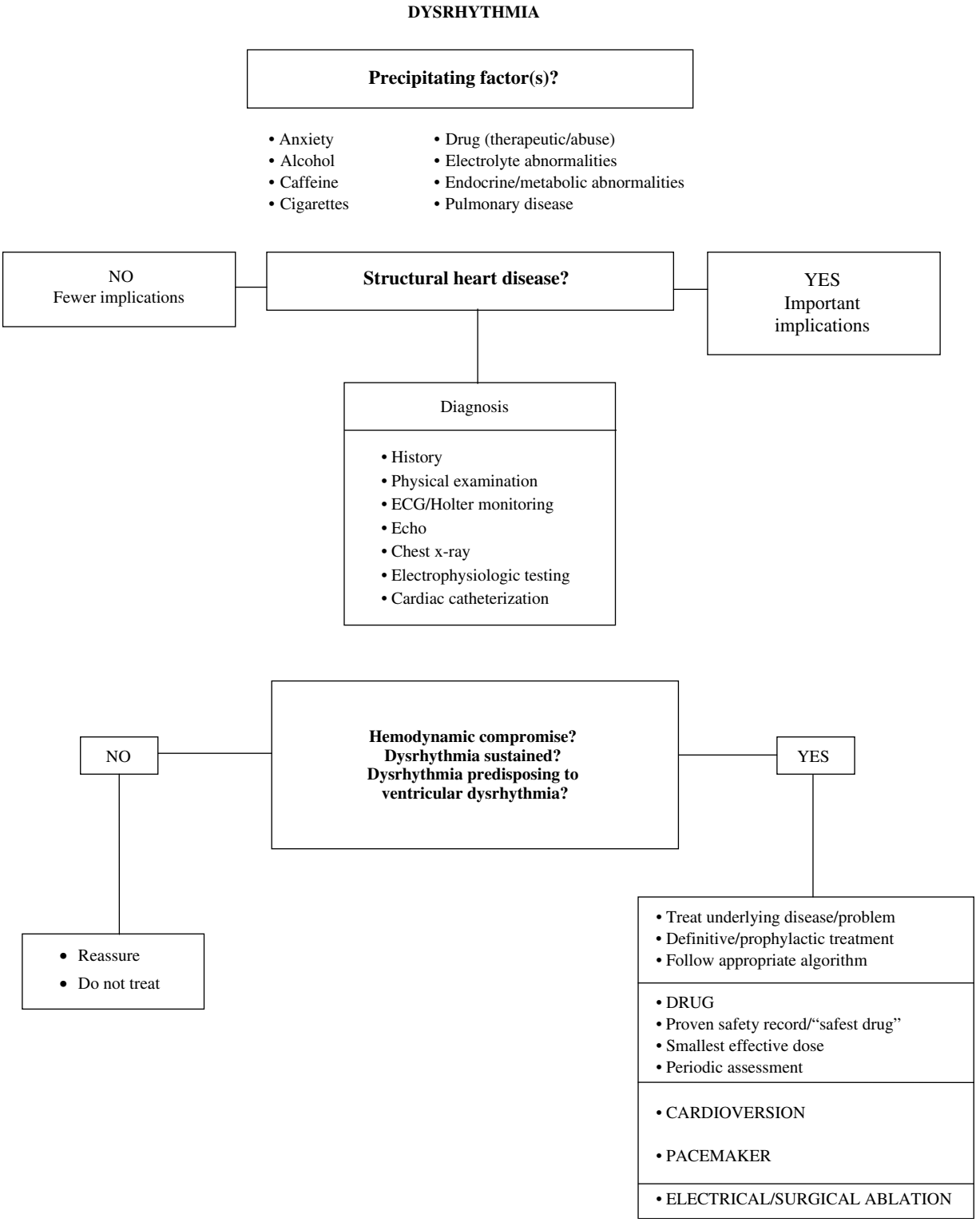

Figure 2.1 Management of dysrhythmias during pregnancy.

cardiac catheterization, and electrophysiologic investigations in order to avoid ionizing radiation exposure, procedure-induced dysrhythmias, and/or hemodynamic compromise. Some radiographic procedures, especially in the first eight weeks of pregnancy, may cause abnormal fetal organogenesis and increased risk of childhood malignancy, particularly leukemia. Serial echocardiographic assessments are useful with minimal maternal and fetal risk (see Table 2.3). Chest radiographs are not ordered routinely but, if required, appropriate pelvic shielding keeps fetal radiation below minimally acceptable levels. When necessary, right

Table 2.3 Noninvasive echocardiography assessment during pregnancy

Two-dimensional echocardiography	Evaluation of LA dilation or thrombus
Doppler echocardiography	Transmitral gradients
	Mitral valve areas
	Using atrioventricular pressure gradient half-time
	Two-dimensional exam technically inadequate
	Previous commissurotomy
	Densely calcified leaflets
	Intracardiac pressures (RV and PAP) if tricuspid regurgitation
Transesophageal echocardiography	Visualization of thrombi (usually in LA appendage)

LA = left atrium; RV = right ventricle; PAP = pulmonary artery pressure

heart catheterization can be performed without fluoroscopy, using a flow-directed catheter. Nuclear studies have little place in pregnant women.

Sinus node dysrhythmias

1. **Sinus tachycardia** occurs when the sinus node discharge rate is >100 bpm. It is characterized by a gradual onset and offset and is due to acceleration of Phase 4 diastolic depolarization of the sinus node pacemaker cells. Sinus tachycardia may result from a primary disorder of the sinus node (sinus node reentry). Sinus tachycardia may be seen during pregnancy, especially in the third trimester (earlier in twin pregnancy) and at delivery without any pathological significance. Sinus tachycardia is usually a physiological response and treatment is rarely needed. If associated with an underlying pathological state (e.g. fever, hemorrhage), the underlying problem should be treated.
2. **Sinus bradycardia** is defined as a sinus node rate < 60 bpm. It may be physiologically normal, especially in the physically fit parturient, or abnormal, occurring in association with many contributing factors outlined in the Advanced Cardiac Life Support (ACLS) Bradycardia Algorithm.[12] If there is hemodynamic compromise, follow the ACLS bradycardia algorithm with respect to treatment.[12]

   Parturients receiving spinal anesthesia for C/S may develop sudden, severe bradycardia and hypotension. This may be due to a rapidly ascending sensory block (> T2), with blockade of cardioaccelerator fibers. In some individuals, it seems to be associated with predominant vagal tone, and atropine may be required in addition to volume expansion and vasopressors.
3. **Wandering pacemaker** is the result of shifting of the dominant pacemaker from the sinus node to latent pacemakers in the atria or atrioventricular junction. It rarely requires treatment.
4. **Sinus node dysfunction/sick sinus syndrome (SSS)** incorporates a range of abnormalities of sinus node impulse formation and conduction including sinus bradycardia, sinus arrest, sinus exit block, sinoatrial and atrioventricular conduction disorders, paroxysms of alternating rapid, regular, or irregular atrial tachydysrhythmias with bradydysrhythmias. Although more usual in the elderly, SSS may occur in patients under age 30.[13] The incidence of SSS during pregnancy is unknown. Treatment depends on the dysrhythmia. Permanent pacing may be necessary for bradydysrhythmias, and drug therapy may be required for tachydysrhythmias. Schatz and colleagues described a primigravida with Ebstein anomaly who had a severe bradycardia-junctional tachycardia syndrome requiring multiple drug treatments and temporary transvenous pacing during delivery.[14] Mendelson described a 32-year-old woman who had occasional syncope associated with sinus exit block. Pregnancy did not affect the frequency of syncopal episodes and no therapy was required. She had three normal term deliveries.[15]

Atrioventricular (AV) blocks

Atrioventricular blocks, (first-, second-, third-degree), may be caused by medications, electrolyte abnormalities, or structural problems such as those resulting from acute MI and myocarditis.[13]

First-degree AV block

A prolonged PR interval (>0.20 s) is found in approximately 0.5% of the normal population and may be secondary to increased vagal tone, drugs, ischemia, and/or rheumatic heart disease.[4] During pregnancy, first-degree AV block usually results from rheumatic heart disease, but if there is no underlying pathology it is usually benign.

Second-degree AV block

Mobitz type I (Wenckebach) second-degree AV block is characterized by a progressive lengthening of the PR interval until an impulse is blocked (i.e. no QRS follows the blocked P wave). The block is at the AV node, is often transient, and may be asymptomatic. The condition is relatively benign and may occur during sleep or whenever vagal tone is increased. It is commonly seen in association with rheumatic fever, ischemia, and inferior wall MI, and it may result from medication. The block seldom progresses to complete AV block.[4] Treatment with pacing in patients with Mobitz type I block is indicated only in seriously symptomatic patients.

Mobitz type II second-degree AV block is characterized by the sudden stopping of an impulse without previous prolongation of the PR interval. The block is most often below the AV node at the bundle of His or at the bundle branches. The block is often

symptomatic with the potential to progress to complete (third-degree) AV block. When it occurs in the presence of acute MI, it is usually associated with larger infarcts and higher morbidity. An accompanying bundle branch block (BBB), frequently involving the His-Purkinje system, may be seen on EKG. Permanent pacing is recommended for pregnant women with symptomatic Mobitz type II AV block.[4]

The incidence of second-degree AV block during pregnancy is very low. The majority of cases reviewed by Mendelson[15] were acquired, occurring in association with rheumatic heart disease and infection. Among 26 cases of acquired heart block, six had second-degree AV block. In another study, only 1 of 21 non-pregnant women with congenital heart block had a second-degree block.[16]

Third-degree AV block

Third-degree AV block (complete heart block) occurs when no supraventricular impulses are conducted to the ventricles. The block may occur at the level of the AV node, bundle of His, or bundle branches. No impulses pass between the atria and ventricles. Complete AV dissociation is present, with the atrial and ventricular rates determined by their own independent pacemakers. The ventricular rate is usually low (junctional = 45–50 bpm; idioventricular rate = 35–45 bpm) and the atrial rate faster. Congenital third-degree AV block is often nodal, resulting from an immunologic attack by maternal antibodies on the fetal AV node.[17] Acquired third-degree AV block is usually infranodal, involving the His-Purkinje system. Third-degree heart block may be permanent, or transient, depending on the underlying cause.

The first case of complete heart block in pregnancy was reported in 1914. Mendelson[15] analyzed 40 reported cases of complete heart block in pregnancy. Twenty women had acquired AV block: secondary to rheumatic heart disease (11), infection (6), myocarditis (2), and coronary artery disease (1). In the other 20 women with congenital heart block, 10 had a VSD. The maternal and fetal mortality rates were 13% and 15%, respectively.

Maternal and fetal prognosis for women with complete heart block is improved due to artificial pacemakers.[18] Women with congenital complete heart block (see Table 2.4) and normal QRS duration are usually asymptomatic and have uneventful pregnancies,[19] in contrast to those with acquired heart block.[4] Heart block, by itself, rarely affects the course or outcome of pregnancy if the ventricular rate remains in the range of 50–60 bpm. If the rate slows suddenly, syncope may occur. Stokes-Adams attacks, and limited HR responses to stress, may occur and women with these symptoms may require a temporary pacemaker for labor and delivery. Permanent AV sequential pacing is a desirable option in symptomatic women.[4] Pregnancy is usually well tolerated in women with pacemakers.

Right bundle branch block (RBBB)

In RBBB there is delay in activation of the RV while septal and left ventricular (LV) activation are normal. The QRS is prolonged (>0.12 s), an "M"-shaped complex is seen in V1 and V2 and a broad S wave is present in the LV leads, especially lead I. Right bundle branch block may be the result of an isolated congenital lesion, RV hypertrophy or strain, myocardial damage, or disease of the specialized conducting tissues.

Table 2.4 Congenital complete heart block in pregnancy

Incidence = 1:15 000–1:22 000 live births
ECG criteria for diagnosis (usually narrow QRS)
Slow pulse from an early age
No history of infection (diphtheria, rheumatic fever, etc.)
No evidence of ischemic heart disease or cardiomyopathy
No history of cardiac surgery
May present during pregnancy

Left bundle branch block (LBBB)

In leads V5 and V6, the small negative Q wave normally seen is replaced by a large, positive R wave and a secondary R wave ("M"-shaped ventricular complex), and QRS > 0.12 s. Left bundle branch block may occur because of myocardial damage secondary to coronary artery disease or cardiomyopathy, LV hypertrophy, or disease of the specialized conduction tissues. Left bundle branch block is rarely seen with an otherwise normal heart and can occur intermittently. Recently acquired LBBB has a poor prognosis.

Left anterior and posterior fascicular blocks (hemiblocks)

The anterior and posterior fascicles of the left bundle branch conduct impulses to the anterosuperior and posteroinferior areas of the LV respectively. Left anterior and posterior hemiblocks are common in conduction tissue diseases.

Management of bradycardia associated with poor perfusion[12]

Transcutaneous pacing should be used without delay for symptomatic unstable women with high-degree (Mobitz type II second-degree or third-degree) block who do not respond to oxygen and atropine. While awaiting a pacemaker, second-line drugs, *dopamine* 5–20 μg/kg/min, *epinephrine* 2–10 μg/min, or *isoproterenol* 2–10 μg/min, may be helpful. If transcutaneous or transesophageal pacing is ineffective because of inconsistent capture, or if effective pacing does not improve the clinical condition because the cardiovascular symptoms are not caused by the bradycardia, consultation and transvenous pacing are the next steps. Atropine should be used cautiously in the presence of coronary ischemia or MI because increased HR may increase ischemia or the zone of infarction. With the trend for women of advanced maternal age (> 35) to bear children, coronary artery

disease and ischemia should be considered in the differential diagnosis.

Ectopic beats

The terms ectopic beat, extrasystole, and premature contraction are synonymous. They refer to an impulse arising from the atria, AV junction (AV node or bundle of His), or ventricles, which arises prematurely in the cardiac cycle.

Premature atrial depolarizations (PAD)

A diagnosis of PAD is made on the ECG when a premature P wave is noted with a P–R interval >120 milliseconds (msec). The interval between the ectopic beat and the preceding beat (coupling interval) is shorter than the cycle length of the dominant rhythm. Usually the contour of a premature P wave differs, indicating a different focus of origin.[20] Sometimes PAD are not conducted to the ventricles or may be conducted with a BBB pattern. Premature atrial depolarizations occur in 20–40% of young healthy individuals[4] and they may be found during routine prenatal examination or an investigation of "palpitations". Isolated PAD were found in 90% of 30 healthy women studied during labor.[8] Contributing factors include stress, anxiety, fatigue, infection, nicotine, caffeine, alcohol, and sympathomimetic asthma preparations or decongestants. Normally, PAD do not require therapy, and avoidance or removal of precipitating factors is often therapeutic. Occasionally, PAD reflect occult heart failure or excessive adrenergic tone when appropriate treatment is diuretics, analgesics, sedatives, or beta-blockade. If PAD are frequent, they may trigger sustained supraventricular or ventricular tachydysrhythmias that require treatment.

Premature ventricular depolarizations (PVD)

The QRS complex of PVD is premature, broad (>0.12 sec), abnormal in shape, and is not preceded by a premature P wave. The most common cause of "palpitations" or "awareness of skipped beats" during pregnancy is PVD as they tend to be noticed more than those caused by PAD. Premature ventricular depolarizations are followed by a compensatory pause only if they are not conducted to the atria. Occasionally, PVD produce distressing symptoms from the increased myocardial contractility associated with the postectopic beat. Clinically, PVD are accompanied by a giant "a" (cannon) wave, visible in the neck as the PVD occurs against a closed tricuspid valve. Sudden distension of the pulmonary veins may elicit an associated spontaneous cough.

Premature ventricular depolarizations occur frequently in the general population. In a Holter monitor study of 50 healthy women, 54% had PVD (6% had >50 beats in 24 hours).[16] Most pregnant women with PVD have no underlying heart disease. Premature ventricular depolarizations may be associated with anxiety, intake of stimulants, infection, electrolyte abnormalities, hypoxia, mitral valve prolapse (MVP), hypertension, congenital heart disease, myocardial ischemia and MI, myocarditis, cardiomyopathy, rheumatic heart disease, long QT syndrome, [4] and a variety of medications, including digoxin.

Indications for treatment of PVD during pregnancy include PVD with hemodynamic compromise, sustained symptomatic PVD, and PVD with an underlying structural abnormality, possibly predisposing to life-threatening dysrhythmia (controversial). Correction of underlying causes and avoidance of stimulants may reduce or eliminate PVD and, generally, pharmacologic therapy is avoided. Quinidine and procainamide (Vaughan Williams Class IA) have a good safety record in pregnancy (FDA Pregnancy Risk Classification – Class C) although the side effects are undesirable. Low-level beta-blockade is as effective as quinidine in suppressing symptoms. Among Class IB antidysrhythmic drugs, the safest appears to be lidocaine (Class IB), provided serum levels are monitored and maternal and fetal effects followed closely. A small subset of women with MVP and LQTS is predisposed to ventricular tachycardia, which, if sustained, may be associated with embolic events and sudden death. A history of PVD and, MVP or LQTS may warrant prophylactic antidysrhythmic treatment. Chronic PVD, which are frequent, multifocal, "R on T", or that occur in salvos, are associated with increased cardiovascular mortality, but there is no evidence that their suppression improves prognosis.[20]

Tachydysrhythmias

Based on the appearance of the QRS complex, the tachycardias are classified into sinus tachycardia, narrow-complex (supraventricular) tachycardia, and wide-complex tachycardia. Most wide-complex tachycardias are *ventricular* in origin. Narrow-complex tachycardias, which are irregular, are usually atrial fibrillation (AF), or possibly atrial flutter, or multifocal atrial tachycardia.

Narrow-QRS-complex tachycardias (SVT)

Supraventricular tachycardia encompasses a variety of tachydysrhythmias originating in the sinoatrial (SA) node, atria, and AV junction. Supraventricular tachycardia is characterized by a narrow QRS (< 0.12 s) complex (except for cases of preexisting BBB or aberrant conduction) with a regular R–R interval and a rate between 150–250 bpm (see Table 2.5) Atrial depolarization is retrograde, resulting in inverted P waves in EKG leads II, III, and aVF. The P wave may occur just before, during, or after the QRS complex, and it is not seen if it arises during the QRS complex. Reciprocating tachycardias involving anomalous (accessory) AV or nodal-ventricular pathways are included even though the atrium and ventricle are part of the reentrant circuit.

Paroxysmal supraventricular tachycardia (PSVT)

If a dysrhythmia is recurrent, starts and stops suddenly, it is designated paroxysmal. Paroxysmal supraventricular tachycardia

Table 2.5 Supraventricular dysrhythmias in pregnancy

Dysrhythmias	Rate/rhythm	P wave/PR	QRS	Clinical importance	Treatment
PAD	Regular with "skipped" beats	P wave contour abnormal; PR >120 ms	Normal	Common (64%) Occasionally may trigger sustained PSVT or VT Underlying heart disease uncommon; Precipitating factors: stress, infection, alcohol, caffeine (tea, coffee, colas), nicotine (cigarettes), stimulant drugs (sympathomimetic asthma medications, decongestants); occult heart failure (very occasionally)	Reassurance Avoid stimulants Usually no drugs required
PSVT	AR 140–220 bpm 2:1 AV block (usual) regular rhythm	? P waves (inverted P in II, III, AvF) PR normal or ↑	Normal or ↑	2.6% pregnancies Usually well tolerated Serious sequelae can occur Can mimic VT if aberrant QRS Abrupt onset & offset	Goal: slow AV conduction: 1. Vagal 2. Drugs 3. Cardioversion
Atrial tachycardia: a. Nonparoxysmal b. Multifocal	AV block	P wave in or follows QRS RP > PR interval	–	Multifocal AT frequently associated with respiratory failure	
Atrial flutter	Type I (classic): AR 300, VR 150; 2:1 AV conduction; Type II: AR >350	Sawtooth flutter waves	Normal	Less common than AF Underlying heart disease usual	1. Rapid atrial pacing (Type I) 2. Drugs (Type II) 3. Cardioversion
Atrial fibrillation	AR 350–600 VR 100–200 Irregular	No P waves	Narrow complexes	Uncommon in pregnancy Can occur in structurally normal hearts (paroxysmal form) Chronic form associated with myocardial and systemic disease	1. Convert to SR: Drugs Cardioversion Pacemaker 2. Slow VR drugs 3. Prevent recurrence Drugs

PAD = premature atrial depolarizations; PR = pulse rate; PSVT = paroxysmal supraventricular tachycardia; VT = ventricular tachycardia; AT = atrial tachycardia; AR = atrial rate; AV = atrioventricular; SR = sinus rhythm; VR = ventricular rate; AF = atrial fibrillation

is a distinct clinical syndrome characterized by repeated episodes (paroxysms) of tachycardia with an abrupt onset, lasting from a few seconds to several hours. Paroxysmal supraventricular tachycardia may stop spontaneously, or it may stop when another ectopic supraventricular beat interrupts the circitous movement.[20]

General mechanisms

Electrophysiologically, SVT is caused by two main mechanisms: (1) reentry; or (2) rapid, abnormal atrial activity (atrial tachycardia, atrial flutter, AF). With reentrant tachycardias, there is an additional electrical connection between atria and ventricles, so that an impulse can circulate between atria and ventricles, repeatedly and rapidly, along a circuit consisting of the AV node junction and the additional AV connection. Additional connections may occur between atria and ventricles. In atrioventricular nodal reentrant tachycardia (AVNRT), the AV node and its adjacent atrial tissues are functionally dissociated into fast and slow AV nodal pathways. In AVNRT, the additional connection is an accessory AV pathway – a strand of myocardium that straddles the groove between atria and ventricles and bypasses the AV node. If the accessory AV pathway can conduct in an anterograde direction (atria to ventricles), the features of Wolff–Parkinson–White (WPW) syndrome are present (see later). More than 90% of PSVT are due to reentry, and the initial event is frequently a PAD. Details of the mechanisms involved can be found in standard cardiology texts.

Clinical presentation

Supraventricular tachycardia has a heterogeneous clinical presentation most often occurring in the absence of detectable heart disease in younger individuals.[11] Patients with paroxysmal dysrhythmias are often asymptomatic at the time of evaluation. A clinical history, describing the pattern in terms of number of episodes, duration, frequency, mode of onset, and possible triggers, is important.

Paroxysmal supraventricular tachycardia-related symptoms include syncope, or near-syncope, distressing palpitations, angina, dyspnea, fatigue, anxiety, and polyuria. Some women with PSVT may be asymptomatic or be aware of palpitations that are not distressing. *Syncope* occurs in approximately 15% of patients with SVT, usually just after initiation of rapid SVT or during a prolonged pause after abrupt termination of the tachycardia. Syncope may be associated with AF, with rapid conduction over an accessory AV pathway, or structural abnormalities such as valvular aortic stenosis, hypertrophic cardiomyopathy, or cerebrovascular disease.[11] *Angina* and *pulmonary edema* may occur in women with heart disease, the symptoms reflecting myocardial ischemia and heart failure, respectively. These latter hemodynamic events result from decreased LV filling and cardiac output.[21] Pulmonary edema is most likely to occur if SVT lasts longer than six hours or in the presence of underlying heart disease, such as mitral stenosis.

Physical examination does not usually lead to a definitive diagnosis. If irregular cannon waves and/or irregular variation in the first heart sound intensity are present, then a ventricular origin of a regular tachycardia is strongly suggested. The presence of associated heart disease should be sought, and an echocardiogram may be helpful.

In pregnancy

The estimated incidence of PSVT during pregnancy is as high as 2.6% but in those with a prior history, episodes may be more frequent and severe.[4,22,23] Often, a diagnosis of PSVT is made for the first time during pregnancy. Paroxysmal supraventricular tachycardia occurs more often during pregnancy in women with a prior history of PSVT, or with WPW syndrome-associated dysrhythmias,[4,22] or in those treated with beta-agonists.[24] The most common cause of a sustained dysrhythmia in pregnancy is reentrant SVT. Paroxysmal supraventricular tachycardia is often called paroxysmal auricular, atrial, or supraventricular tachycardia with the underlying electrophysiologic mechanism rarely defined.[4]

Treatment

In the absence of coexisting heart disease, the majority of SVT of the atrioventricular nodal reentrant type (AVNRT) are well tolerated in young people.[25] When treatment is required for termination of stable reentry SVT, *vagal maneuvers* and *adenosine* are preferred. If the tachycardia has a regular narrow-complex QRS, vagal maneuvers alone (carotid sinus massage, Valsalva maneuver, or gagging) will terminate about 20–25% of reentry SVT.[26] Eyeball massage should *never* be performed because it may result in retinal detachment.[25] If reentry SVT does not respond to vagal maneuvers, current ACLS guidelines[12] recommend adenosine (Class I). Calcium channel blockers (verapamil is more effective than propanolol)[29] have a similar SVT conversion rate to adenosine, but adenosine tends to be more rapid with fewer side effects than verapamil.[12] If the rhythm converts, it was most likely reentry SVT. The woman should be observed for recurrence, and any recurrence treated again with adenosine or a longer-acting AV nodal blocking agent such as diltiazem or a beta-blocker. Amiodarone can achieve nearly 100% efficacy in the inhibition of induced sustained reentrant SVT.[27]

Irregular palpitations are probably due to premature depolarizations, AF, atrial flutter, or multifocal atrial tachycardia.[11] Expert consultation is recommended. The rate may be controlled using diltiazem and/or beta-blockers.

If someone is hemodynamically *unstable* with narrow-complex tachycardia, adenosine can be administered while preparations are made for synchronized cardioversion (10–50 joules, Class IIb). Current recommendations are to proceed quickly to synchronized cardioversion and to not delay in order to establish i.v. access and administer drugs.[12] Various drugs, including adenosine, verapamil, beta-blockers, and Class IA antidysrhythmic drugs, will successfully terminate SVT [21,28,29] with adenosine the drug of choice.[12,28] Cholinergic agents (e.g. edrophonium) and pressor agents (e.g. phenylephrine) are other classes of drugs that are used to stop PSVT in the presence of normal or low blood pressure (BP), respectively.[30] Rapid atrial pacing is also effective in stopping PSVT and may be useful for those cases refractory to drug therapy.[31]

If someone with irregular, narrow-complex tachycardia is *stable*, there is time to obtain a 12-lead EKG and evaluate the rhythm, await consultation, and determine the best treatment option. Irregular narrow-complex tachycardia is probably AF, or possibly atrial flutter, or multifocal atrial tachycardia. Attempts to control the rate with diltiazem or beta-blockers may be successful. It can be difficult to differentiate supraventricular ectopic beats or SVT with aberrant conduction, from ventricular ectopic beats or ventricular tachycardia (VT). The typical narrow QRS complex of PSVT is not seen if a preexisting, or rate-dependent, BBB is present, or if anterograde conduction to the ventricles occurs over an accessory AV nodal pathway, such as a Kent bundle. The clinical importance of differentiating PSVT and VT is considerable. Treatment of rapid, wide, regular QRS tachycardias with agents such as verapamil, in the belief that the rhythm is SVT with aberrant conduction, can have disastrous consequences (precipitate ventricular fibrillation) if the tachycardia is ventricular.

Prevention of PSVT depends on the frequency and severity of attacks. Beta-blockers, amiodarone, or verapamil may be given. In some, pacemaker implantation may be necessary. When appropriate, ablation procedures that destroy part of an accessory reentrant pathway are done and can result in a long-term cure.[25]

Atrial tachycardia and atrial flutter

Atrial tachycardia may be classified as nonparoxysmal atrial tachycardia and multifocal atrial tachycardia, with the latter

commonly seen in patients with severe pulmonary disease. Atrial flutter is less common than AF. Paroxysmal forms of atrial flutter may occur in the absence of structural heart disease, but in its chronic form, atrial flutter is almost always associated with underlying structural heart disease.[4,30] Atrial flutter is frequently unstable, reverting to sinus rhythm or degenerating into AF.[30]

In atrial flutter, the EKG reveals "saw-tooth" morphology in the inferior leads. Atrial flutter is classified into two types: type I (classic), which shows an atrial rate of 300 bpm and ventricular rate of 150 bpm (2:1 AV conduction); and type II, which shows a flat baseline with a positive flutter wave in the inferior leads and a rate usually >350 bpm. Type I disease originates close to the sinus node and activates the right atrium in a counter-clockwise direction. Type II disease appears to originate in the lateral atrial wall, and the depolarization wave occurs usually in a clockwise direction.

In pregnancy

Relatively few cases of atrial flutter have been reported in pregnancy.[4,15,32] Atrial flutter has been reported in association with a wide variety of conditions including hypertensive heart disease, obstructive pulmonary disease, dilated or hypertrophic cardiomyopathy,[4] Graves disease,[15] rheumatic heart disease,[4] and post-surgical correction of congenital heart disease.[4,32]

Treatment

Treatment is dictated by hemodynamic status. Synchronized cardioversion of atrial flutter can generally be achieved with a relatively low energy of 10–25 joules, ideally with i.v. access and conscious sedation.

In hemodynamically stable patients, beta-blocking agents, calcium channel blockers, or digoxin[4] may control the ventricular rate and occasionally terminate the dysrhythmia. After the ventricular rate is controlled, Class 1A drugs (procainamide, quinidine) are commonly required to achieve conversion to normal sinus rhythm. To avoid converting a 2:1 block to 1:1 conduction with an even faster ventricular rate, Class IA antidysrhythmic drugs (e.g. procainamide) should only be administered after the ventricular rate has been controlled.

When there is hemodynamic instability or drug therapy failure, direct current cardioversion, starting with low energy of 10–25 joules, is the treatment of choice for atrial flutter. The need for long-term drug treatment depends on the frequency and severity of the dysrhythmia. Beta-blocking agents, calcium channel blockers (diltiazem, verapamil), or digoxin may be effective.[33] Radiofrequency ablation can potentially cure atrial flutter with success rates in the 80–90% range.[4]

Atrial fibrillation

Atrial fibrillation is characterized by totally disorganized atrial depolarization at a rate of 350–600 bpm. Most atrial impulses are blocked because of concealed conduction within the AV node, and the ventricular rate is irregular at 100–200 bpm. As with atrial flutter, paroxysmal AF can occur in normal hearts, while the chronic form is associated with myocardial and systemic disease (see Table 2.5). In patients with cardiovascular disease, AF is associated with doubling of morbidity and mortality.[34]

The hemodynamic consequences of AF depend on the severity of the underlying disease and the ventricular rate. Atrial fibrillation is more common in patients with enlarged left atria (> 40 mm). In patients with mitral stenosis, a faster HR shortens the diastolic filling time and increases the transvalvular pressure gradient. Sudden onset of AF with rapid ventricular rates raises left atrial pressure, leading to symptoms of dyspnea and possibly pulmonary edema. Because normal left atrial contraction contributes up to 30% of the presystolic, transvalvular pressure gradient, abrupt loss of atrial contraction can decrease cardiac output by 20%. Ventricular filling is restricted more by the rapid HR than by loss of atrial contraction. When LV dysfunction with reduced ventricular compliance is present, cardiac output may drop dramatically.

Embolic stroke and peripheral embolization are more frequent in patients with chronic AF and underlying heart disease (especially mitral stenosis). Clinically evident emboli develop in approximately 35% of patients with mitral valve disease, 18% with ischemia and hypertension, and 10% with hyperthyroidism. Post-mortem examination of patients with chronic AF demonstrates emboli in 45% of those with valvular disease and 35% of those with ischemia and hypertension. The risk of embolization is much less in the absence of heart disease.[4]

In pregnancy

Atrial fibrillation and atrial flutter are rare in women of reproductive age and, therefore, warrant investigation when diagnosed during pregnancy. In the past, reported cases of AF in pregnancy were associated most often with rheumatic heart disease, especially mitral valve disease. In 1956, Mendelson[15] identified 31 women with AF of whom 29 had rheumatic heart disease. Nineteen women had New York Heart Association (NYHA) class III and IV disease, and the associated maternal and fetal mortality was 19% and 58% respectively. Five women had embolic complications.[15] Fifty years ago the prevalence of rheumatic heart disease was higher than it is today. Today, AF occurs more frequently with congenital and valvular heart disease and occasionally with pulmonary embolism, acute myocarditis or pericarditis, cardiomyopathy, rheumatic heart disease, and alcohol or drug abuse.[4] However, AF secondary to rheumatic disease still occurs in areas of the world where women are deprived of health care and sanitary living conditions. In a report of recurrence rates of dysrhythmias during pregnancy and the early postpartum period,[37] AF or atrial flutter recurred in 52% of the 23 pregnancies studied.[35] In six women with AF or atrial flutter at baseline all remained in that rhythm throughout pregnancy. Adverse fetal events occurred in 20%, independent of other maternal or fetal risk factors, and were

more common in women who developed recurrent antepartum dysrhythmias.[35]

Treatment

Initially, correct any contributing or underlying cause, followed by either conversion of the dysrhythmia to sinus rhythm, or slowing of the ventricular response when conversion does not occur. Intravenous drugs used to convert acute AF include esmolol, procainamide, and amiodarone. Esmolol and amiodarone are pregnancy category C and D drugs, respectively, meaning they should only be given if the potential benefit justifies the potential risk to the fetus. Digitalis, calcium channel blockers, and/or beta-blockers are given to control the HR in chronic AF that does not convert to sinus rhythm. In the operating room and intensive care unit, i.v. calcium channel blockers and beta-blocking drugs are useful because they quickly slow ventricular response, although they do not restore normal sinus rhythm. *Beta-blockers are the preferred drugs for acute ventricular rate control in women with AF during pregnancy.* [36] Digoxin is not as effective in the acute setting, because it requires more than one hour to slow ventricular response significantly. Adenosine slows ventricular response briefly, aiding in the diagnosis but not the treatment of AF. If AF is part of a tachycardia–bradycardia syndrome, pacing may be required in addition to drug therapy.

Electrical cardioversion (100–360 joules) is reserved for patients who are unstable or unresponsive to drug therapy.[36] The decision to proceed to electrical cardioversion should be made after careful evaluation of underlying heart disease, duration of AF, left atrial size, and condition of the mother and fetus. Successful conversion and sustained sinus rhythm are most likely in patients with small left atria and AF of less than several months' duration. Administration of procainamide or quinidine (after digitalization) for a few days before electrical cardioversion is recommended, because 10–15% of cases convert to sinus rhythm during this time. Despite successful conversion, hemodynamic improvement may not be seen immediately as left atrial contraction may remain depressed for several weeks.[20] Long-term therapy with flecainide, sotalol, disopyramide, propafenone, and amiodarone may be required to prevent recurrence of AF.[22] Calcium channel blockers that affect the AV node are deleterious in patients with AF or flutter associated with preexcitation (e.g. WPW).

The incidence of embolization during cardioversion is 1–3%. If elective cardioversion is planned, consideration should be given to thromboembolic prophylaxis. Anticoagulation is recommended in the presence of mitral stenosis; in recent-onset AF of more than four days' duration; and in association with a history of recurrent and recent emboli, prosthetic mitral valve, and dilated cardiomyopathy. If not contraindicated, anticoagulation for two weeks before and four weeks following cardioversion significantly decreases systemic embolization.[4] Long-term anticoagulation is recommended for individuals with persistent AF. Warfarin is associated with spontaneous abortion in 10–50% of pregnancies and multiple teratogenic effects.[4] As a result, low molecular weight heparin has become a commonly used anticoagulant during pregnancy.

Wide-complex tachycardia

Ventricular tachycardia

Electrocardiographic features of VT include bizarre QRS complexes longer than 120 ms, fusion beats, capture beats, and AV dissociation occurring at a rate of 100–250 bpm. Fifty percent have retrograde conduction to the atria. Occasionally, differentiation from a wide-QRS tachycardia of supraventricular origin may be difficult and expert consultation is advisable. For example, rapid AF with conduction over a bypass tract appears as a grossly irregular, rapid (200–300 bpm), wide-QRS tachycardia on EKG. Vagal maneuvers or drug therapies that slow conduction over the AV node may help in the differential diagnosis. Occasionally, electrophysiologic testing may be required. Wide-QRS tachycardia of uncertain origin should be considered as VT until proven otherwise, and it should be treated accordingly (i.v. amiodarone, synchronized cardioversion). Nonsustained VT is defined as VT that does not cause hemodynamic compromise and stops spontaneously in <30 s. Sustained VT is defined as VT that lasts >30 s or that which causes hemodynamic compromise and requires immediate termination.[4]

Ventricular tachycardia develops by one of three mechanisms: (1) reentry; (2) abnormal automaticity; and (3) triggered activity. Triggered activity occurs when the impulse is the result of early or delayed after-depolarizations. Calcium ions and slow, inward calcium channels are involved in the latter, and calcium channel blocking drugs (e.g. verapamil) may be helpful. Triggered activity also may be involved in dysrhythmias associated with congenital or acquired LQTS or excess catecholamines.[4] Ventricular tachycardia may occur in the absence of any obvious structural cardiac abnormalities (primary electrical disease). Ventricular tachycardia in pregnancy usually fits into this category with some episodes arising for the first time during pregnancy.[37,38,39,40,41] Typically, VT originates from the RV outflow tract or LV septal region.

Factors known to precipitate paroxysmal VT include physical exertion, emotional upset, fear, exercise, caffeine, smoking, alcohol, trauma, changes in posture, hypokalemia, hypomagnesemia,[42,43,44] and imbalance of the autonomic system.[45] Clinically, VT usually presents with symptoms of rapid palpitations, chest discomfort, and dizziness. Syncope or sudden death may be the initial manifestation, especially in the presence of structural heart disease and/or a very rapid VT rate.

Some catecholamine-sensitive, nonsustained VT can be prevented by treatment with beta-blocking drugs and avoidance of exercise and other triggers. Ventricular tachycardia in the presence of underlying structural heart disease has a poorer prognosis.

In pregnancy

Ventricular tachycardia is rare in pregnancy and usually occurs in the absence of structural heart disease. Ventricular tachycardia has been reported with structural heart disease including congenital heart disease, RV dysplasia, MVP, LQTS, acute myocarditis, cardiomyopathy, cardiac tumors, and coronary artery disease.[4]

About 30 case reports of VT in pregnancy appeared in the literature between 1942 and 1992.[4] Overall, maternal outcome is good but cardiac deaths have occurred.[46,47] Careful evaluation to determine the cause of VT may identify a correctable cause such as hypomagnesemia-induced recurrent sustained VT.[42,43] One woman with VT died during her sixth month of pregnancy, three weeks after initiation of procainamide,[48] and another with hypertrophic cardiomyopathy died from VT at 39 weeks' gestation.[49] Paroxysmal VT in women without demonstrable heart disease is reported to be more frequent in pregnancy but evidence is limited. It also is unclear as to whether there is a pattern of variability during different trimesters.[4]

Treatment

If VT is well tolerated hemodynamically, the drug of choice in current ACLS[12] protocols is amiodarone. There are concerns about the safety of amiodarone in pregnancy. It currently is classified as a Food and Drug Administration (FDA) Class D drug. Lidocaine (FDA Class B) and procainamide (FDA Class C), considered safer during pregnancy, successfully terminate the majority of VT. If VT is unresponsive to drug therapy or is associated with hemodynamic compromise, direct-current cardioversion (50–300 joules) is indicated. Low-energy synchronized shock (20–50 joules) is often successful in restoring normal sinus rhythm. In those individuals with a history of sustained VT or who are symptomatic with frequent episodes of nonsustained VT, correction of an identified precipitating factor or long-term antidysrhythmic medication may be necessary.[4] Some antidysrhythmic medications increase the propensity to other dysrhythmias (prodysrhythmia), and these may increase the risk of sudden death. Drugs currently considered to have less prodysrhythmic potential include beta-blockers and amiodarone. The risks and benefits of each medication must be assessed on an individual basis.

Ventricular fibrillation

Ventricular fibrillation (VF) should be treated according to the current ACLS protocol,[12] always with care to maintain left uterine displacement to ensure adequate venous return.

Dysrhythmias associated with heart disease

Heart disease is classified as either congenital or acquired. Advances in the medical and surgical management of children with congenital heart disease (CHD) have resulted in an increasing number of affected females reaching childbearing age (see Chapter 1). From 1970 to 1983, CHD increased from 20% to 42% as a cause of heart disease complicating pregnancy. A dysrhythmia during pregnancy may be the presenting complaint that leads to a diagnosis of previously unrecognized CHD. Women with uncorrected ASD may develop supraventricular dysrhythmias during pregnancy. Dysrhythmias associated with CHD[50,51] are outlined in Table 2.6 and those associated with acquired structural heart disease are outlined in Table 2.7.

Table 2.6 Dysrthythmias associated with congenital heart disease in pregnancy

Heart defect	Dysrhythmia
Atrial septal defect	Supraventricular dysrhythmias
Congenital heart block	Bradydysrhythmias
Ebstein anomaly	Supraventricular dysrhythmias
Eisenmenger syndrome	Sudden death
Mitral valve prolapse	Atrial & ventricular dysrhythmias
Tetralogy of Fallot	Conduction system disorders
	Heart block
	Bradycardia
	Ventricular dysrhythmias
Transposition of the great arteries[53]	Loss of sinus rhythm
	Supraventricular dysrhythmias
	Heart block
Tricuspid atresia	Atrial fibrillation
Double outlet right ventricle or	Sinus bradycardia
Single ventricle	Complete AV block

AV = atrioventricular

Specific lesions

Ebstein anomaly

Women with Ebstein anomaly are at risk for reentrant paroxysmal tachycardia, often via a bypass tract as seen in WPW syndrome. The course of the pregnancy is determined by the severity of the tricuspid regurgitation, stenosis, and right-to-left shunting across the ASD. This anomaly is usually mild in adults and some women remain asymptomatic, successfully completing pregnancy. Cyanosis may appear for the first time during pregnancy. Right ventricular failure can occur from an increase in tricuspid regurgitation. After surgical tricuspid valve reconstruction, pregnancy may result in worsening of residual tricuspid regurgitation, dysrhythmias, and endocarditis. Epidural anesthesia has been used successfully for C/S and labor analgesia in women with Ebstein anomaly (see Chapter 1).

Eisenmenger syndrome and pulmonary hypertension

Death may occur suddenly in patients with Eisenmenger syndrome, although symptomatic dysrhythmias generally occur late in the natural history of the disease. Pregnancy is not tolerated well (50% maternal mortality; $>40\%$ fetal mortality), and consideration may be given to first trimester termination of pregnancy.

Surgically repaired Tetralogy of Fallot (TOF)

Important postoperative electrophysiologic sequelae, including bradycardia, conduction system disease, heart block, ventricular dysrhythmias, and sudden death, have been reported following

Table 2.7 Dysrhythmias associated with structural heart disease in pregnancy

Aortic valve disease	Ventricular dysrhythmias
	PVD (84%)
	Multifocal PVD, couplets, runs of ventricular tachycardia (73%)
	Aortic stenosis ↑ risk of severe hemodynamic problems with atrial fibrillation or junctional rhythm (loss of atrial contraction)
	Avoid volatile anesthetic-induced junctional rhythms
	Supraventricular dysrhythmias with atrial dilation
	CHF + dilated cardiomyopathy
	– PVD (80%)
	– Nonsustained ventricular tachycardia (50%)
	– Decreasing heart chamber size may decrease atrial and ventricular dysrhythmias
IHSS	Sudden death
	Ventricular tachycardia
Ischemic heart disease	Ischemia/coronary vasospasm
	Atrial dysrhythmias
	Ventricular dysrhythmias
	Anti-ischemic therapy (nitroglycerin) may be therapeutic and more efficacious than antidysrhythmics
Mitral stenosis	Atrial fibrillation
	Decreased LV filling/cardiac output
	Increased LAP & LA volume → CHF
	Thrombus formation atrial appendage
Mitral valve prolapse	Atrial dysrhythmias (PSVT)
	Ventricular dysrhythmias
	Prolonged Q-T
	Avoid hypovolemia and vasodilatation (decrease LV size; ↑ prolapse)
Pericarditis	Atrial dysrhythmias
	ECG changes:
	– Low voltage QRS complexes
	– Electrical alternans
	– ST segment elevation (diffuse)
	– T wave inversion
	– PR segment depression
Peripartum cardiomyopathy	Dysrhythmias common
	ECG:
	– Nonspecific ST-T changes
	– Infarct pattern
	Avoid hyperkalemia (can exacerbate dysrhythmias)

PVD = premature ventricular depolarization; CHF = congestive heart failure; IHSS = idiopathic hypertrophic subaortic stenosis; LAP = left atrial pressure; LA = left atrial; PSVT = paroxysmal supraventricular tachycardia

repair of TOF.[50] Affected patients should be evaluated periodically for the presence of serious dysrhythmias.

Transposition of the great arteries

Most people with transposition of the great arteries (TGA) undergo surgical repair before reaching childbearing age. Although atrial switch is rarely performed today except as part of a "double switch" operation, there continues to be interest in pregnancy outcome in Mustard and Senning repair survivors who are at risk from heart block, ventricular dysrhythmias, and sudden death. In a large report from Holland looking at the risk of complications during pregnancy after a Mustard or Senning repair, there was a high incidence of obstetric complications and mortality in the offspring.[51] The most important cardiac complication was clinically significant dysrhythmia (22% of subjects) especially if there was a prior history of dysrhythmia. Preterm delivery was common and 22% of the offspring were small for gestational age. However, no recurrence of congenital heart disease was documented in the offspring.[51]

Tricuspid atresia, double-outlet right ventricle, and single ventricle

The electrophysiologic sequelae of surgical repairs include AF, sinus bradycardia, and complete AV block.[50] In preconception counselling, these women should know that dysrhythmias may increase during pregnancy.

Mitral valve prolapse (MVP)

Mitral valve prolapse is usually benign. However, atrial and ventricular dysrhythmias occur with greater frequency in women with MVP, especially if there are resting ST segment and T wave abnormalities (see Table 2.8). Paroxysmal supraventricular tachycardia involving AV nodal reentry or accessory AV connections (see later) is the most common tachydysrhythmia. A very small subset of patients with a diagnosis of MVP and LQTS may have a predisposition to VT, which can result, rarely, in sudden death.

Dysrhythmias associated with cardiac transplantation

The transplanted heart is denervated (see Chapter 22). Although the transplanted heart shows an increased sensitivity to catecholamines, normal vagal tone and reflex activity are lacking. Normal contractility is present, but chronotropic responses to stress and exercise are altered. The HR increase with exercise may be delayed and initial adaptation occurs as a result of the Frank-Starling mechanism. The usual decrease in HR during recovery is attenuated. Dysrhythmias may result from the increased sensitivity to catecholamines or be a manifestation of rejection. Only direct-acting agents will exert inotropic or chronotropic effects. Atropine should be used with caution and

Table 2.8 Mitral valve prolapse in pregnancy

Associated conditions	Clinical importance	Course
Accessory AV connections (WPW syndrome and variants)	Prolapse aggravated by hypovolemia and vasodilatation	Benign
ASD	Atrial dysrhythmias (PSVT)	Progressive degeneration of mitral valve
Ebstein anomaly of tricuspid valve	Ventricular dysrhythmias	Mitral regurgitation
Hypertrophic cardiomyopathy		Complex dysrhythmias
Marfan syndrome		
Ostium secundum		
Long Q-T syndrome (↑ risk VT)		

AV = atrioventricular; WPW = Wolff–Parkinson–White; ASD = atrial septal defect; VT = ventricular tachycardia; PSVT = paroxysmal supraventricular tachycardia

appropriate monitoring; however, it is likely to be ineffective because the transplanted heart lacks vagal innervation. Paradoxical slowing and high-degree AV block have been reported.[12]

Dysrhythmias associated with electrolyte abnormalities

Potassium

Ventricular dysrhythmias may occur with serum potassium (K^+) levels < 3.0 mEq/l. Hypokalemia and hypomagnesemia may attenuate the effects of antidysrhythmic drugs. The serum K^+ level should be kept > 4.0 mEq/l.

Magnesium

Low serum magnesium (Mg^{2+}) levels reduce sodium (Na^+)–potassium (K^+) pump activity. This results in increased Na^+/calcium (Ca^{2+}) exchange, raises intracellular Ca^{2+} levels, and reduces intracellular K^+ concentrations. It is difficult to restore intracellular K^+ in the presence of low Mg^{2+} levels. Chronic Mg^{2+} depletion may occur with diuretic and aminoglycoside therapy, alcohol abuse, secondary aldosteronism, and malabsorption syndromes. Serum Mg^{2+} levels may not accurately reflect intracellular Mg^{2+} levels, especially in chronic depletion. Reduced intracellular Mg^{2+} decreases extrusion of Ca^{2+} (via the calcium–adenosine triphosphatase pump), resulting in increased Ca^{2+} currents, which are dysrhythmogenic in triggered automaticity models.

Clinical reports suggest that Mg^{2+} deficiency is linked with cardiac rhythm disturbances including PVD, supraventricular and ventricular dysrhythmias, and Torsade de Pointes.[43] Magnesium therapy reduces the incidence of supraventricular and ventricular dysrhythmias following MI and cardiac bypass surgery. Magnesium is also beneficial in digitalis toxic dysrhythmias, Torsade de Pointes, and refractory ventricular dysrhythmias, even when the serum Mg^{2+} level is within normal limits. Two grams of magnesium sulfate i.v., given over two to three minutes, can be used to treat ventricular dysrhythmias refractory to lidocaine and procainamide.[44]

Preexcitation syndromes

Definition

Preexcitation results when an impulse, originating in the atrium, activates (depolarizes) the ventricular myocardium (whole or in part) earlier than expected. The clinical syndromes that accompany short PR intervals and anomalous QRS complexes are shown in Table 2.9. Collectively they constitute the preexcitation syndromes.[52] The incidence of preexcitation in the normal population is 0.01% to 0.3%, but it occurs with increased frequency in MVP [53] and Ebstein anomaly. In the majority of cases there is no evidence of underlying heart disease. Ten percent of individuals with recurrent PSVT have WPW syndrome.

Pathophysiology

Normally the atria become electrically isolated from the ventricles during fetal development. Incomplete separation leads to an accessory AV pathway, which may be situated anywhere across the groove between the atria and ventricles. The most common site is the left free wall of the heart, but other locations include posteroseptal, right free wall and anteroseptal. In a minority, there is more than one accessory pathway.[20]

To facilitate the most common form of AV reentrant tachycardia it is *only* necessary for the accessory pathway to conduct in a retrograde direction, from ventricles to atria. Many individuals with AV reentrant tachycardia have an accessory AV pathway, which is only capable of ventriculoatrial conduction. In those with WPW syndrome, the pathway is *also* capable of anterograde conduction, that is from atria to ventricles. Unlike the AV node, the accessory connection does not delay conduction between atria and ventricles. During sinus rhythm, an atrial impulse reaches the ventricles by both the accessory pathway and the AV node. The AV node conducts relatively slowly. Initial ventricular activation is due to conduction via the accessory pathway, resulting in a shortened PR interval (ventricular preexcitation). Because the accessory pathway is not connected to specialized conducting tissue (His–Purkinje system), early activation is slow, resulting in a slurring of the

Table 2.9 Preexcitation syndromes

Type	EKG	Dysrhythmias	Clinical implications	Treatment
Wolff–Parkinson–White (WPW) syndrome Type A: premature excitation of LV Type B: premature excitation of RV	Short PR < 120 ms wide QRS > 120 ms delta wave; ST-T directed opposite delta wave + QRS vectors	Recurrent tachydysrhythmias: 14–90% WPW = AV reentrant tachycardia, atrial fibrillation, or atrial flutter Most often precipitated by premature beat arising in atria, ventricle or AV junction	May be asymptomatic but with typical ECG pattern; ↑ frequency dysrhythmias in pregnancy Associated conditions: MVP Ebstein anomaly, balloon mitral valve +/– mitral insufficiency, ASD/form fruste cardiomyopathy Fetus with WPW predisposed to dysrhythmias in utero	1. PSVT with wide[a] QRS: suspect AF/flutter DC cardioversion (50–100 joules) or i.v. sotalol, flecainide, disopyramide, or amiodarone ([a]adenosine contraindicated) 2. Surgical interruption of accessory pathway after epicardial mapping (when not pregnant)
Lown Ganong Levine & variants	PR usually short; QRS normal; Refractory period normal or decreased	Variety of tachydysrhythmias can be life-threatening: – Tachycardia with regular narrow QRS – AF with rapid ventricular response – VT/VF		1. AV reentrant tachycardia (PSVT) with narrow QRS: i.v. adenosine or verapamil (Alt: digoxin, propranolol) 2. Cryoablation of AV node–His bundle
Nodoventricular + Fascioventricular		Reentrant tachycardias	Associated condition(s): Ebstein anomaly	

AF = atrial fibrillation; AV = atrioventricular; MVP = mitral valve prolapse; ASD = atrial septal defect; DC = direct current; i.v. = intravenous; VT = ventricular tachycardia; VF = ventricular fibrillation PSVT = paroxysmal supraventricular tachycardia

ventricular complex (delta wave). During sinus rhythm, the ventricular complex is a fusion between the delta wave and normal QRS complex.

EKG findings

The typical EKG in WPW syndrome shows a shortened PR interval < 120 ms with a slurred upstroke (delta wave) and broadened QRS complex and ST-T waves directed in the opposite direction from the QRS vector (see Figure 2.2).

Associated dysrhythmias

Approximately two-thirds of individuals with preexcitation develop cardiac dysrhythmias during their life. The incidence of supraventricular dysrhythmias in women with WPW syndrome may increase during pregnancy.[54] Two dysrhythmias occur with WPW syndrome: AF and, more commonly, atrioventricular reentrant tachycardia.

When AF (350–600 impulses/min) occurs in individuals *without* preexcitation, the AV node protects the ventricles from rapid atrial activity. Individuals with WPW syndrome who develop AF can have very fast ventricular rates, as the accessory pathway can conduct very quickly. The EKG will show a totally irregular ventricular response characteristic of AF. The shape of some of the ventricular complexes will be normal, but most ventricular complexes will show delta waves. A very rapid ventricular response to AF can lead to heart failure, shock, and an increased risk of VF. Ventricular fibrillation is usually seen when the interval between delta waves during AF is < 250 ms. The risk of VF is very low in individuals who are asymptomatic and in those with intermittent accessory pathway conduction.

Usually the AV node recovers before the accessory pathway after excitation. If an atrial ectopic beat arises during sinus rhythm when the AV node has recovered but the accessory pathway has not, the resulting ventricular complex will be narrow and not have a delta wave. By the time the PAD has traversed the AV junction and ventricles, the accessory pathway will have recovered and be able to conduct the impulse back to the atria. When the impulse reaches the atria, the AV junction will again be able to conduct and the impulse can repeatedly circulate between atria and ventricles, leading to an *AV reentrant tachycardia*. Similarly, a ventricular ectopic beat during sinus rhythm can be conducted to the atria via the accessory pathway and initiate AV reentrant tachycardia. The EKG will show narrow ventricular complexes (unless there is a rate-related BBB) in

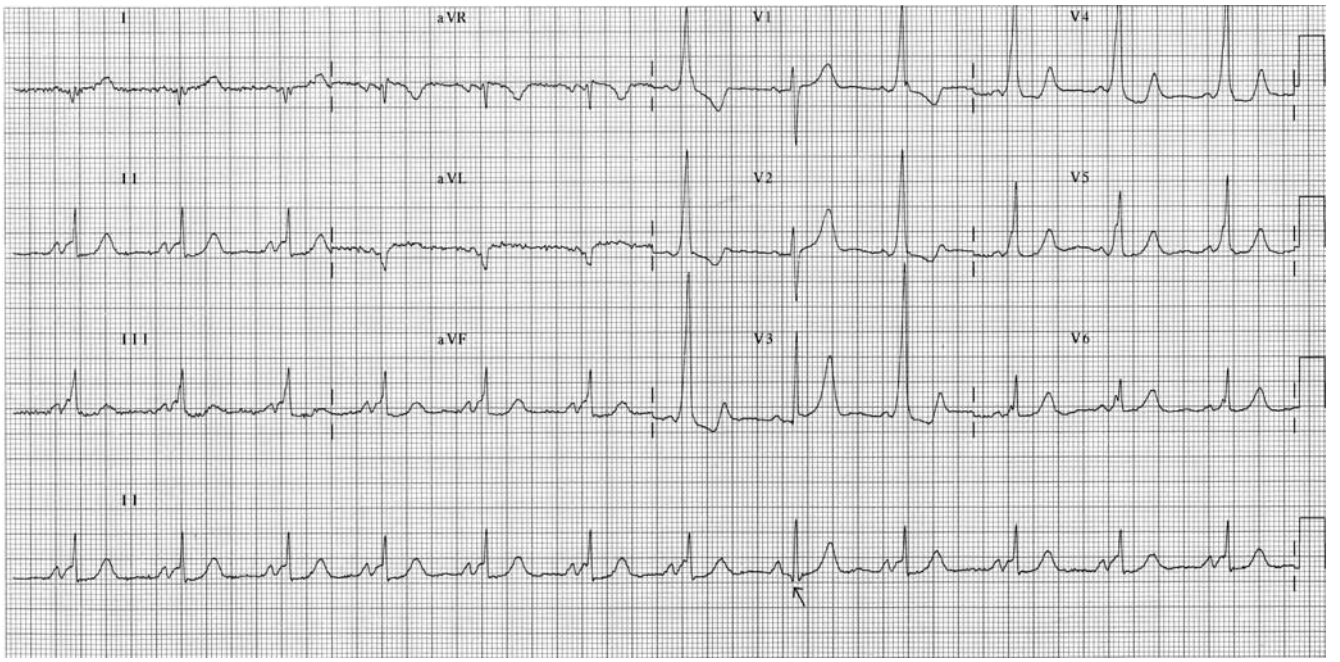

Figure 2.2 EKG of patient with Wolff–Parkinson–White syndrome.

rapid regular succession. Unlike AF, there will be no delta waves, and there will be no clue from the ventricular complexes that WPW syndrome is present. This is termed *orthodromic* AV reentrant tachycardia (anterograde conduction via normal AV node pathway, retrograde conduction from ventricles to atria via accessory pathway). *Antidromic* AV reentrant tachycardia, much less common, occurs when anterograde conduction from atria to ventricles is over the accessory pathway and return to the atria is via the AV pathway. The ventricular complexes will be in the form of large delta waves.

In pregnancy

As noted earlier, pregnancy may predispose women to the development of tachydysrhythmias. Women with known WPW syndrome whose condition has been stable during the nonpregnant state can develop dysrhythmias during pregnancy.[54,55,56,57,58] It is important to monitor the at-risk parturient sufficiently to identify a tachydysrhythmia, as well as monitor the fetus to detect adverse fetal effects from a dysrhythmia.

Treatment

Radiofrequency ablation of the accessory pathway should be considered in all symptomatic individuals, especially if drug therapy is ineffective or cannot be tolerated, or if there is a fast ventricular response to AF.[55] Occasionally, ablation is indicated in an asymptomatic individual when the consequences of developing a serious dysrhythmia might jeopardize their safety or that of others by nature of their occupation. The success rate for radiofrequency ablation procedures is high and the risks are low.

During AV reentrant tachycardia (orthodromic type), there are no delta waves and no evidence from the ventricular complex of preexcitation. Treatment is the same whether or not there is preexcitation. Vagal stimulation (carotid sinus massage, Valsalva maneuver) is chosen frequently as the initial treatment for AV reentrant tachycardia, followed by adenosine (see Table 2.10).

During AF associated with WPW syndrome, most of the ventricular complexes are broad due to presence of large delta waves. If the hallmark of AF (totally irregular rhythm) is ignored, the rhythm may be mistaken for VT. Most atrial impulses are conducted to the ventricles via the accessory AV pathway during AF. Cardioversion is the simplest method for termination of AF and has been used successfully, with no adverse effects on pregnancy, mother, or fetus, with the exception of transient fetal dysrhythmias.[56] If AF recurs frequently, cardioversion is not appropriate and a drug that will slow conduction in the accessory pathway, such as sotalol, flecainide, disopyramide, or amiodarone, is recommended. These drugs slow the ventricular response to AF and frequently restore sinus rhythm.[20] Digoxin and verapamil should be avoided because they may increase conduction through the accessory pathway, increase the ventricular rate, and precipitate VF. The risk of VF is increased when the minimum interval between delta waves during AF is < 250 ms.[20]

Anesthetic implications

Tachydysrhythmias may develop during anesthesia in individuals with known WPW and other preexcitation syndromes. Women presenting for anesthesia with an established tachycardia are, of course, best treated by first correcting the dysrhythmia. In general, agents and techniques likely to cause undue tachycardia and circulatory disturbance should be avoided.

Table 2.10 Treatment of WPW dysrhythmias

Atrioventricular reentrant tachycardia	Atrial fibrillation (AF)
	ECG: broad ventricular complexes (large delta waves) + totally irregular rhythm (can be mistaken for VT)
	Risk of VF during AF when < 250 ms between delta waves
Treatment:	*Treatment:*
1. Vagal stimulation	1. Cardioversion: simplest, safest method to terminate AF (unless frequently recurrent)
2. Drugs: adenosine, verapamil	2. Drugs: ibutilide (acute conversion of AF, FDA approved), amiodarone, sotalol, flecainide (slow conduction in the accessory pathway)
3. DC cardioversion (with sedation or GA)	*Avoid* AV nodal blocking drugs (digoxin, verapamil, beta-blockers) which ↓ refractory period in accessory pathway,↑ ventricular rate and may precipitate VF
4. Pacing (overdrive or programmed stimulation)	
Prevention:	*Prevention:*
1. Drugs: amiodarone, sotalol, flecainide	1. Ablation of accessory pathway Consider in all symptomatic patients (success-rates high, risks low)[22]
2. Ablation of accessory pathway Consider in all symptomatic patients (success-rates high, risks low)[22]	

WPW = Wolff–Parkinson–White; DC = direct current; GA = general anesthesia; VT = ventricular tachycardia; VF = ventricular fibrillation

Table 2.11 LQTS: classification and etiology

Congenital syndromes	Jervell, Lange-Nielsen syndrome (autosomal recessive)
	Romano-Ward syndrome (autosomal dominant)
Acquired	
Electrolyte abnormalities	Hypokalemia, hypomagnesemia, hypocalcemia
Malnutrition or liquid-protein diet	
Drugs:	*Antidysrhythmics:*[a]
Cardiac	Class Ia agents: quinidine, procainamide, disopyramide
	Class Ic agents: flecainide, encainide, indecainide, lidocaine
	Class III agents: amiodarone, sotalol
	Coronary vasodilator: prenylamine
Anesthetic	Thiopental, succinylcholine, epinephrine, norepinephrine
Psychotropic	Phenothiazines, tricyclics, tetracyclic drugs
Miscellaneous	Organophosphate insecticides, other
Central nervous or autonomic system injury	Intracranial, subarachnoid hemorrhage
	Acute cerebral thrombosis
Cardiac diseases	*Bradydysrhythmias*:
	sick sinus syndrome, high-grade AV block
	structural heart disease
	ischemic heart disease, mitral valve prolapse
	cardiomyopathy, myocarditis, ischemia
Metabolic abnormalities	Hypothyroidism, hypothermia

[a] Vaughan Williams classification of antidysrhythmic drugs
LQTS = Long QT syndrome; AV = atrioventricular

Avoiding aortocaval compression is important. The effects of such an obvious insult to cardiac output, especially if the woman is already compromised by a tachydysrhythmia, can be disastrous.

Long QT syndrome

Long QT syndrome (LQTS) refers to a heterogeneous group of disorders (see Table 2.11) that have in common a prolonged QT interval on EKG and a propensity to a particular type of VT called Torsade de Pointes (TdP). Cardiac output and BP tend to fall dramatically with resultant syncope. Most tachydysrhythmic episodes stop spontaneously with return of consciousness, but some may degenerate into VF and result in sudden cardiac death. Ventricular dysrhythmias and symptoms are frequently triggered by increased sympathetic activity associated with acute emotional or physical distress.

QT interval prolongation and TdP are more common in women, possibly due to gender differences in ion channels.[59] The baseline QT interval is longer in women than in men. TdP associated with QT prolongation appears related to estrogen levels and is more frequent in menstruating women. Women appear to be especially susceptible to QT prolongation from drugs and the incidence of TdP associated with medications (e.g. quinidine, class III antidysrhythmics, tricyclic antidepressants) appears higher in women.[59,60] The degree of QT prolongation does not seem to have any prognostic value.

Long QT syndrome is now understood to be a collection of genetically distinct dysrhythmogenic cardiovascular disorders resulting from mutations in the genes encoding the ion channels responsible for three of the fundamental ionic currents in the cardiac action potential.[61] More than 35 mutations in 4 cardiac ion channel genes have been identified, and currently molecular genetic testing is available for the KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 genes.[62,63] LQTS has a prevalence of 1:1100 to 3000.[65] Long QT syndrome is categorized as inherited (Jervell, Lange-Nielsen syndrome, Romano-Ward syndrome) or acquired.

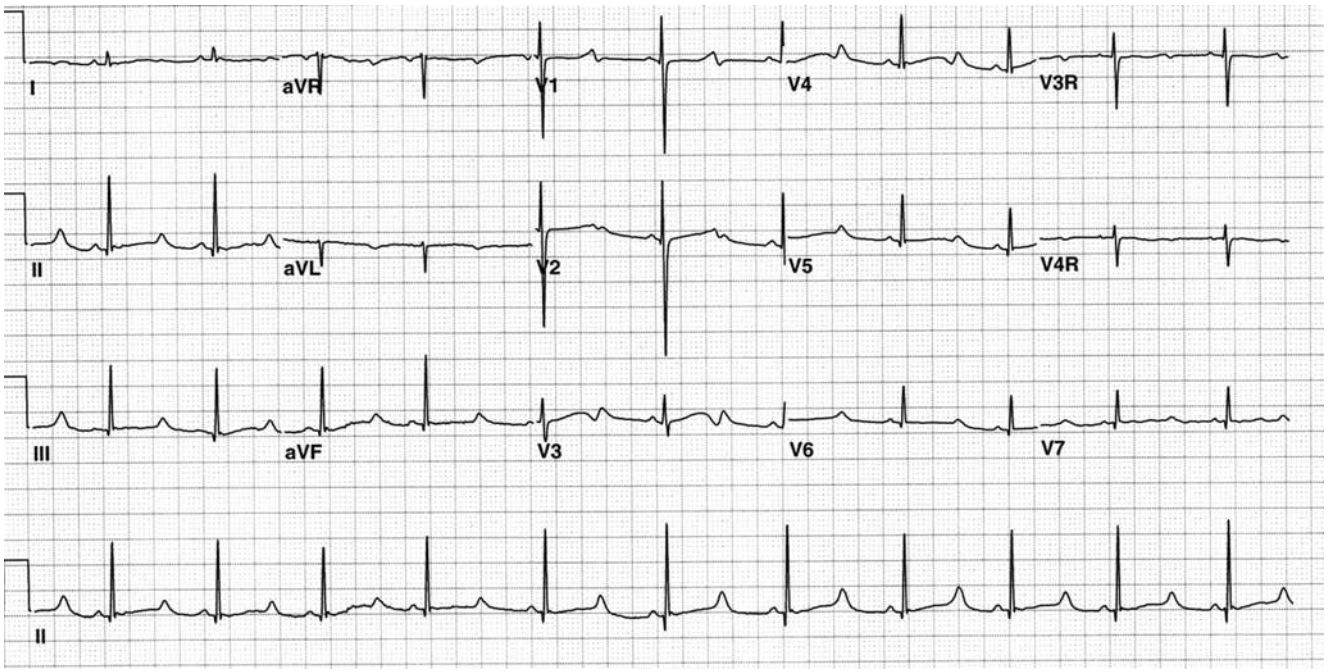

Figure 2.3 EKG of patient with long QT interval.

The "acquired" group are now considered to be silent mutation carriers in whom a specific trigger unmasks the condition.[65]

The diagnosis of LQTS is based on clinical history, family history, and EKG. Long QT Syndrome is symptomatic in approximately 60% of patients. Clinical symptoms include syncope (26–30%), seizure (10%), and cardiac arrest (9%), usually secondary to adrenergic arousal. In the 40% who are asymptomatic, diagnosis is based on a family history or EKG and/or gene testing.[63] A positive family history includes a history of sudden cardiac death in an immediate family member before age 30, or a family member with a confirmed diagnosis of LQTS. Women with a history of unexplained syncope, documented polymorphic VT, or a family history of sudden cardiac death, should be carefully screened for this disorder. At a minimum, this screening would entail obtaining an EKG and a more detailed family history.[59]

QT interval

Prolongation of the QT interval is defined as a QT interval corrected for HR (QTc) >440 ms for males, and >460 ms for postpubertal females (see Figure 2.3). Optimal measurement of the QT interval, which varies with HR and autonomic tone, is obtained during a resting state with simultaneous recording of several limb leads, and measurement of the QT interval in lead II (if T wave amplitude is reasonable). Using Bazett's formula, the QTc is obtained by dividing the measured QT interval by the square root of the preceding R–R interval in seconds. The measured QT interval may also be compared against Simonson's age-and-rate adjusted normal range of values of the QT interval.[66]

A prolonged QT interval is generally taken to represent abnormal repolarization of cardiac muscle, and it is during the vulnerable relative refractory period of ventricular repolarization that ventricular dysrhythmias are most easily triggered. The QT interval normally shortens with increasing HR and shows circadian periodicity with a nadir during sleep and a peak shortly after awakening, corresponding to the hours when the risk of sudden cardiac death is highest.[67]

Torsade de Pointes

A small minority of patients with QT prolongation from any cause are at risk for developing TdP. Torsade de Pointes is characterized by phasic changes in amplitude and polarity of the QRS complexes so that the peaks appear to be twisting around an imaginary isoelectric baseline (twisting of the points).

Jervell, Lange-Nielsen syndrome (JLNS)

This syndrome, first described in 1957,[68] is characterized by long QTc, (usually >500 ms), bilateral sensorineural deafness, and an autosomal recessive pattern of inheritance involving the KCNQ1 and KCNE1 genes.[62] A deaf child experiencing syncope during physical exertion, fright, or stress is the typical presentation of this syndrome. The syncopal episodes and occasionally sudden death, result because of triggered ventricular tachydysrhythmias (VT, VT–TdP, VF) occurring in association with the prolonged QT interval.[69]

Romano–Ward syndrome

This syndrome, described in 1963 by Romano and in 1964 by Ward, refers to individuals with normal hearing who have the same prolonged QT interval, T wave abnormalities, propensity to develop syncope associated with ventricular tachydysrhythmias

(VT–TdP, VT, VF), as seen in JLNS. The pattern of inheritance is autosomal dominant with varying expression.[63] Cardiac events, more common from the preteen years through the 20s, may occur at any age, from infancy onward.[63] The fetus, due to genetic dominance, has a 50% probability of inheriting the disorder.[63]

Management of these two syndromes is directed toward preventing syncope, cardiac arrest, and sudden death. Current recommendations include avoidance of activities known to precipitate syncope and avoidance of drugs known to prolong the QT interval. Current therapies include beta-blocker therapy, insertion of cardiac pacemakers and implantable cardiac defibrillators.

Acquired LQTS

Triggers for QT prolongation and TdP

Prolonged QT can be precipitated by drugs, electrolyte disturbances, hypothermia, and any cause of sympathetic stimulation (Table 2.11).[65]

Increased caution is recommended when treating women (pregnant and nonpregnant) with antidysrhythmic drugs. Class Ia drugs (quinidine, procainamide, disopyramide) cause TdP with equal frequency.[66] Class Ic drugs (flecainide, encainide, indecainide, lidocaine), Class III drugs (amiodarone, sotalol), and prenylamine (coronary vasodilator) produce TdP less commonly.[66] Torsade de Pointes has not been reported with Class Ib drugs, which shorten the QT interval, or with beta-adrenergic blockers or calcium antagonists. In about half of the patients, drug-induced TdP occurs within the first three to four days of initiation of therapy, but late onset occurrence (months to years later), usually in association with a change in drug dose, electrolyte imbalance, or a bradydysrhythmia, is also seen.[67] Warning signs of an impending drug-induced TdP may be the new appearance of a peculiar ventricular bigeminy with late cycle PVD and bizarre postpause T wave changes in association with a moderate QT prolongation.[66] Phenothiazines and tricyclic antidepressant drugs, similar to quinidine electrophysiologically, increase the duration of the QRS complex, prolong the QT interval, and cause T wave flattening with U wave prominence. These EKG changes occur in about 50% of patients treated with phenothiazines (thioridazine > chlorpromazine or trifluoperazine) and about 20% of patients treated with tricyclic antidepressants. Increased ventricular irritability is a potential complication with therapeutic as well as toxic doses of these psychotropic drugs. Although the risk of TdP is relatively low, it has been documented to occur with the majority of psychotropic drugs, thioridazine being implicated most often. Episodes of TdP are often preceded by abrupt sympathetic activation, such as might occur with anger, fright, or sudden awakening.

Long QT syndrome is sometimes associated with central nervous system diseases such as intracranial aneurysms, subarachnoid hemorrhage, acute cerebral thrombosis, and brain metastases. Torsade de Pointes can also be precipitated by severe hypokalemia and severe hypomagnesemia alone or in combination, and hypokalemia in combination with antidysrhythmic or psychotropic drug therapy. Although hypocalcemia may prolong the QT interval, it is seldom associated with the development of TdP. Torsade de Pointes is a rare complication of liquid-protein modified-fast dieting in individuals who have had significant rapid weight loss over a short period of time and exhibit QT prolongation on EKG. Bradydysrhythmias can also cause TdP. Ventricular dysrhythmias (some TdP in morphology) are implicated as a cause of syncope in 10% to 60% of patients with high-grade AV block and syncope, and in 4% to 7% with sick sinus syndrome and syncope. Some patients with MVP, who also have QTc prolongation, have a higher prevalence of ventricular dysrhythmias.

Treatment

Treatment options include beta-blockers, pacemaker, automated internal cardioverter-defibrillator (AICD), and/or left cervicothoracic sympathectomy. Untreated symptomatic LQTS is estimated to have >20% mortality rate in the first year of diagnosis. Schwartz reported a decrease in mortality from 71% in untreated patients to 6% in patients treated with beta-blockers.[70] However, beta-blocker therapy was ineffective in approximately 25% of cases.[70]

The goal of treatment is to prevent and treat any dysrhythmia that can result from prolonged QT interval. Immediate therapy should include withdrawal of the offending agent(s) and correction of any underlying electrolyte abnormality, hypothermia, and cause of sympathetic stimulation. Failure to diagnose LQTS may lead to continued use of the offending agent as well as administration of antidysrhythmic drugs capable of further prolonging the QT interval, thus increasing the risk of developing a fatal dysrhythmia.

Beta-blockers are the first line of treatment. Beta-blocker therapy plays a significant role in effectively suppressing ventricular dysrhythmias, which are often precipitated by sympathetic activity. In someone with LQTS, suppression of PVD may be beneficial as PVD may be a precursor of TdP or VT. In full doses, beta-adrenergic antagonists completely suppress or significantly reduce the frequency of symptoms, although the QT interval remains unaffected. A “full” (maximum) dose of propranolol is that which is tolerated, or produces symptomatic bradycardia. Atenolol is a longer-acting cardioselective beta-blocker with fewer side effects than propranolol.

A permanent pacemaker, programmed to prevent bradycardia and pauses (anti-bradycardia pacing), which have the potential to trigger a dysrhythmia, can be helpful when used in conjunction with beta-blocker therapy.[71] Temporary overdrive pacing is a form of emergent therapy in the presence of a life-threatening dysrhythmia.

An AICD is indicated when symptoms (e.g. syncope) persist, and dysrhythmia is documented despite beta-blocker therapy, or when the initial presentation is cardiac arrest.[72] An AICD reduces the incidence of sudden death when the episode of TdP is prolonged or proceeds to VF. Continuation of beta-blocker therapy is recommended when an AICD has been implanted.[72,73] In parturients with a pacemaker or an AICD, the usual precautions should be taken to obtain a full history

Table 2.12 LQTS: treatment in pregnancy

Clinical state	Treatment	Goal of treatment
Congenital LQTS		
Benign LQTS – Asymptomatic (no syncope history) + no family history of sudden death or complex ventricular dysrhythmias	No prophylactic treatment	1. ↓ excess sympathetic activity 2. Prevent and suppress ventricular tachydysrhythmia 3. Maintain uteroplacental perfusion
Asymptomatic with family history of premature sudden death or complex ventricular dysrhythmias	Full dose[a] *beta-blocker*	
Symptomatic LQTS a. ≥1 episode of syncope without prior treatment b. Recurrent syncope despite beta-blocker ± left cervicothoracic ganglionectomy c. Sustained life-threatening dysrhythmia (acute situation)	a. Full dose beta-blocker b. Consider pacemaker c. Temporary overdrive pacing	
Drug-refractory LQTS syncope despite intensive drug therapy or disabling drug side effects	Left cervicothoracic sympathetic ganglionectomy Chronic overdrive cardiac pacing	
Recurrent cardiac arrest	AICD	
Acquired LQTS		
Induced change in ECG pattern: prolonged QTc interval (≥ 440 ms), ↑ PVD ± bigeminy, VT, Torsade de Pointes	Discontinue causative drug Correct underlying electrolyte & metabolic abnormalities (hypokalemia, hypomagnesemia, hypocalcemia)	Early recognition Treat cause Avoid drugs & conditions which cause QT prolongation +/or potentiate ventricular dysrhythmias
Sustained Torsade de Pointes	Electrical defibrillation	
Prevention of recurrent malignant ventricular dysrhythmias	Isoproterenol infusion Cardiac pacing	

[a] Full dose: beta-blockers should be administered to the maximum tolerated dose/symptomatic bradycardia
LQTS = Long QT syndrome; AICD = automatic implantable cardioverter defibrillator; ECG = electrocardiogram; PVD = premature ventricular depolarization; VT = ventricular tachycardia

about the device and consult with the manufacturer or cardiologist about management of the device throughout pregnancy, especially peripartum.

Left cervicothoracic sympathectomy is reserved for patients who are refractory to other types of treatment.[65] Genotype-directed therapy is under investigation as a future treatment option. Any episode of TdP should be treated by cardioversion, defibrillation, and magnesium sulfate.

In pregnancy

Over 900 cases of LQTS have been described in the literature, but there are relatively few reports of LQTS in pregnancy.[64,74,75,76,77,78,79,80,81,82] One study has shown that women with LQT1 caused by the common KCNQ1-A341 V mutation are at low risk for cardiac events during pregnancy especially if beta-blocker therapy is used.[79] Cesarean section was more likely if the neonate was a carrier of the same mutation.[79] Interpretation of fetal cardiotocographic monitoring during possible fetal distress may be difficult when full doses of beta-adrengergic blocking drugs are administered to the mother, or when there is a possibility that the fetus may have inherited the cardiac conduction defect. Monitoring for fetal acidosis with periodic fetal scalp sampling may be the only way to adequately diagnose fetal distress. Neonatal bradycardia and hypoglycemia secondary to beta-blockade should be anticipated and managed as necessary. The treatment of LQTS is summarized in Table 2.12.

Anesthetic management of the parturient with LQTS

Booker has reviewed the principles of anesthetic management of the patient with LQTS (Table 2.13).[65] It is important to reduce emotional stress and anxiety because high levels of circulating catecholamines can precipitate dysrhythmias in patients with

Table 2.13 LQTS in pregnancy: anesthetic considerations

ASSESSMENT	
1. Establish whether congenital or acquired long QT syndrome (LQTS)	1. Continue (or establish) appropriate treatment.
2. Assess status: a. electrolytes b. temperature c. blood pressure d. pain e. physical/emotional stress & anxiety	2. Avoid triggering cardiac dysrhythmias & increasing catecholamine (CA) levels: a. correct hypokalemia, hypomagnesemia, hypocalcemia b. correct hypothermia c. avoid/correct hypotension (left uterine displacement, hydration, vasopressors) d. adequate pain relief e. avoid sudden loud noises, vigorous physical exertion (sudden demands for maximal performance) in congenital LQTS f. provide information, reassurance, emotional support g. deaf signage if needed (Jervell, Lange-Nielson syndrome (JLN)) h. judicious use of anxiolytics.
3. History drugs known to cause QT interval prolongation: a. antidysrhythmics b. psychotropic drugs c. anesthetic drugs	3. Avoid or use cautiously: a. quinidine, procainamide, disopyramide, flecainamide, encainamide, indocainamide, lidocaine, sotalol, prenylamine b. phenothiazines, tricyclic antidepressants, lithium c. thiopental (minimal QT prolongation), succinylcholine, norepinephrine, ephedrine.
4. History ventricular dysrhythmias +/– bradydysrhythmias	4. Anticipate & be prepared to treat with drugs, defibrillation, overdrive pacing.
LABOR AND DELIVERY	
1. Monitors & special preparation	1. Monitor mother & fetus, continuous monitoring if symptoms or dysrhythmia; defibrillator on standby: immediately available.
2. Interpretation of fetal cardiotocographic monitoring	2. Fetal heart rate (FHR) & pattern may reflect beta-blocker therapy (or other antidysrhythmic drug) or possible inherited LQTS abnormality. Fetal scalp sampling may be required to establish fetal acidosis & diagnose fetal distress.
3. Left uterine displacement	3. Avoid aortocaval compression.
4. Effects of therapy on fetus & newborn	4. Diagnosis of fetal distress from FHR may be difficult, may need fetal scalp sampling. Treat neonatal bradycardia, hypoglycemia if indicated.
REGIONAL ANESTHESIA	
1. Sympathetic nervous system blockade	1. Advantageous (decreases catecholamine (CA) levels); avoid relative parasympathetic overdrive – sudden bradycardia (PR prolongation).
2. Hemodynamic stability	2. Avoid precipitous drop in BP, use direct & indirect vasopressors judiciously to avoid triggering dysrhythmias & consequences of hypotension.
3. Lumbar epidural anesthesia	3. Titrate local anesthetic cautiously. Allows more hemodynamic stability. Avoid epinephrine with local anesthetic or take precautions.
4. Subarachnoid block	4. Quality/density of block usually better (less pain). Block level less predictable & less controllable. May be more hypotension – treat judiciously. Treat significant bradycardia immediately with atropine/ephedrine.
GENERAL ANESTHESIA	
1. Rapid sequence induction & intubation	1. Minimize CA response; beta-blocker useful (topical/i.v. lidocaine may prolong QT interval).
2. Catecholamine increases	2. Maintain adequate depth of anesthesia; avoid hypoxia, hypercarbia, hypotension.
3. Myocardial sensitization to CA	3. Avoid halothane.
4. Drugs with sympathomimetic properties	4. Avoid or use cautiously ketamine, pancuronium, atropine.
5. Drugs with documented safety in LQTS	5. Thiopental (minimal QT prolongation; clinically insignificant), vecuronium, fentanyl, isoflurane.

CA = catecholamine.

LQTS. Drugs and techniques that minimize catecholamine release and cardiac sensitization to catecholamines should be selected. For those individuals who are profoundly deaf (JLNS), effective communication and reduction of stress and anxiety may be enhanced by an interpreter skilled in deaf signage. Treat conditions known to aggravate QT prolongation, (e.g. hypokalemia, hypomagnesemia, hypocalcemia) and avoid drugs like procainamide, quinidine, lidocaine, droperidol, ondansetron, and phenothiazines.

A combined spinal epidural technique has been used for vaginal delivery in a woman with LQTS.[81] The intial QTc was > 600 ms and remained prolonged at 560 ms after 11 months' therapy with atenolol. There were no untoward effects from the neuraxial analgesia technique.[81]

In another report, spinal anesthesia normalized the QTc that had been prolonged in women with severe preeclampsia.[82] It was postulated that hypertension in pregnancy may be associated with hypocalcemia that in turn prolongs the QT interval; sympathetic blockade from spinal anesthesia was thought to be responsible for shortening the QTc.[82]

Pacemakers and related devices in pregnancy

Women with pacemakers have conceived and carried pregnancies to completion successfully. Also, pacemakers have been implanted during pregnancy with good maternal and fetal outcomes. Current pacemakers and related devices provide more sophisticated support of the cardiovascular adaptations imposed by pregnancy than in the past. For example, rate-responsive pacemakers, programmed to sense a variety of stimuli (e.g. muscle activity, minute ventilation) in addition to atrial and ventricular activity, respond by raising the HR when increased cardiac output is needed.[83]

Pacemakers in pregnancy[84,85,86,87,88,89]

A parturient is most likely to present with or require a pacemaker or pacemaker-related device (e.g. an implantable cardiac defibrillator (ICD)) for definitive or prophylactic treatment of: (1) an intrinsic or surgically-induced *second-degree (type II) or third-degree heart block*; (2) a symptomatic, hemodynamically significant *bradydysrhythmia* or *tachydysrhythmia* (recurrent or unresponsive to drugs); or (3) a *potential life-threatening dysrhythmia*. In a pregnant woman such dysrhythmias or conduction problems are likely seen in conjunction with an intrinsic cardiac condition (congenital, rheumatic or ischemic heart disease, a preexcitation syndrome, LQTS) or in association with a cardiac surgical procedure. Pacemaker therapy is occasionally chosen because of drug refractoriness or intolerance to side effects.

Pacemaker/ICD-associated complications in pregnancy

The probability of successful completion of pregnancy with a pacemaker is favorable. Although uncommon in pregnancy (approximately 25 reports in the literature since 1962), there have been documented problems associated with pacemakers (see Table 2.14).[88] Appropriate recognition and treatment of these complications is essential to ensure optimal maternal and fetal outcomes.[89,]

Anesthetic management of the parturient with pacemaker/ICD

These patients require careful evaluation of their general status, review of cardiac history, specifically reviewing their underlying heart disease, looking for new or recurrent cardiac signs and symptoms (chest pain, confusion, dizziness, shortness of breath, syncope).[83] A thorough assessment of pacemaker type and function should be performed (see Tables 2.15, 2.16). Depending on the pacemaker type (e.g. antitachycardia pacemaker) and programming, special adjustments may be required. Interference from electrical sources (cautery, transcutaneous electrical nerve stimulation) or from other stimuli (shivering, excess catecholamines, temperature) may have important consequences (see Table 2.17). Consultation with a cardiologist regarding appropriate programming is beneficial. Generally speaking these patients benefit from good analgesia during labor. Epidural analgesia decreases catecholamines and allows flexibility if an operative delivery is required.

Table 2.14 Pacemaker associated complications in pregnancy

1. Discomfort at implantation site
2. Ulceration at implantation site
3. Pacemaker failure
4. New signs and symptoms
   a. dizziness (exertion/rest)
   b. dyspnea (exertion/rest)
   c. pulmonary edema
   d. dysrhythmia
   e. extrasystoles
   f. tachycardia
5. Intrauterine growth restriction
6. Fetal dysrhythmia

Table 2.15 Review of pacemaker function

Assessment	Rationale
1. Indications	Optimize pacemaker functioning to meet ↑ demands antepartum, labor/delivery, postpartum
2. Signs/symptoms at time of insertion	
3. Course to date	
4. Type, model, response mode(s) of pacemaker (*see patient identification card if available*)	
5. Pulse generator: replacement date (5–10 year life span device and operation mode(s))	
6. Date pacemaker most recently evaluated	

Antidysrhythmic drugs

Important considerations when using antidysrhythmic drugs in pregnancy and lactation are:

- adjustments in drug dosage necessitated by changes in maternal physiology
- effect of antidysrhythmic drugs on maternal hemodynamics and placental perfusion

Table 2.16 Anesthetic assessment: pacemaker function

Component	Potential problems	Action
Pulse generator pocket	Discomfort at implantation site Ulceration at implantation site May become mobile/loose with external manipulation	Identify problems with generator pocket (implantation site)
Location:		
Pectoralis muscle (sc pocket) left or right subclavian area	Usual location unless myopotential inhibition has been a problem	Note location of pulse generator Relocate appropriately if necessary
Abdomen LUQ	Not an appropriate location during pregnancy	
Pulse generator (PG)	Malfunction	Review EKG for appropriate sensing, pacing, capture[a]
size/shape (usual = 2″ × 5″)		
Components		
Microchip (contains program)	Capture problems Sensing problems	Confirm capture by demonstration of a pulse simultaneously with EKG Avoid absorption of toxic amounts of LA, which can lead to loss of capture
Battery (= most of unit); runs the microchip	Battery failure Competitive inhibition (electromagnetic interference) Transcutaneous electrical nerve stimulators (TENS) Electrocautery Peripheral nerve stimulators	Replace battery if battery is known to be at end of life or soon due for elective replacement Avoid or use very cautiously: Magnet in presence of electromagnetic interference TENS Electrocautery Peripheral nerve stimulator
Epicardial leads	Lead displacement/fracture: ↑ likelihood with newly-placed or temporary leads/trauma Common sites: Lead/PG connection Insertion into subclavian vein Clavicle/1st rib	If necessary, chest x-ray[b] can identify: number, position, integrity of pacing leads Pacemaker ID code Caution re: PAC monitoring with recently inserted pacemaker leads Ensure external pacemaker leads well insulated from contact with any source of potential current leakage
Rate-responsive pacemakers (PM)	Competitive sensing/capture	Know how PM is programmed re: response mode(s)
Stimuli sensing options: Muscle activity – responsive MV(TV + RR) – responsive Evoke QT– responsive Temperature-responsive RV dP/dT (preload/afterload)	Fasciculations, shivering, seizures Positive pressure ventilation CA triggered "R on T" Body temperature changes Hemodynamic changes	Beware potential problems, make appropriate adjustments & verify PM function afterward Avoid shivering/fasciculations; avoid succinylcholine except RSI; NDMRs preferable; RA not contraindicated Control TV + RR Minimize CA discharge Keep temperature normal Consult cardiologist re: appropriate programming

[a] Capture may be confirmed by demonstration of a pulse simultaneously with EKG monitoring.
[b] Chest x-ray used in pregnant women only when definitely indicated.
sc = subcutaneous; LUQ = left upper quadrant; ID = identification; MV = minute volume; TV = tidal volume; RR = respiratory rate; RV = right ventricle; CA = catecholamine; RA = regional anesthesia; LA = local anesthetic: NDMR = nondepolarizing muscle relaxants; PAC = pulmonary artery catheter

Table 2.17 Anesthetic management: parturient with pacemaker

PROBLEM	MANAGEMENT
Pain (↑ CA levels)	Provide adequate pain relief Comfort measures and relaxation techniques TENS; Nitrous oxide/oxygen Narcotics (IM, i.v., i.v.-PCA) Regional anesthesia (LEA; SAB) General anesthesia
Monitors & special preparation	Continuous cardiac monitoring of mother and fetus Pulse oximetry (SaO_2); ABG; FSS prn Alternative or emergency methods of pacing immediately available Cardiologist available (PM malfunction; complications)
Antitachycardia pacemakers	May sense ESU/other intraoperative stimulating devices (misinterpret stimuli as cardiac activity) Cardiologist consultation/involvement in care Decision re: deactivation antitachycardia function preop

CA = catecholamine; TENS = transcutaneous nerve stimulation; IM = intramuscular; i.v. = intravenous; i.v.-PCA = intravenous patient-controlled analgesia; LEA = lumbar epidural analgesia; SAB = subarachnoid block; ABG = arterial blood gases; FSS = fetal scalp sampling; PM = pacemaker; ESU = electrosurgical unit; prn = as necessary

Table 2.18 FDA classification of drugs[38]

FDA category	Definition
A	Well conducted human studies have failed to demonstrate any effect on the fetus in any trimester.
B	No evidence of risk in humans. Animal studies indicate no effect with human studies lacking, or animal studies indicate some harm not confirmed in human studies.
C	Adequate human studies are lacking, and animal studies have shown adverse effects. Possibility of adverse effects.
D	Human studies indicate fetal risk. However, the benefits may outweigh risks in pregnant women.
X	Contraindicated in pregnant women. Human or animal studies indicate substantial fetal risk outweighing the potential benefits.

FDA = Food and Drug Administration

- placental transfer and direct effects on the fetus
- potential for teratogenicity
- secretion in breast milk.

Experience with the use of some antidysrhythmic drugs in pregnancy, especially the newer ones, is limited. Based on the evidence available, the FDA has graded antidysrhythmic drugs according to the relative safety of their use in pregnancy (see Table 2.18). The risk of pro-arrhythmia with both class IA and III antidysrhythmics is the most worrisome side effect for mother. For this reason it is recommended that continuous ECG monitoring be used when therapy with these drugs is initiated, and that the need for drug therapy be reassessed on a regular basis.[90,91] Drugs commonly used to treat dysrhythmias during pregnancy are summarized in Table 2.19.

Adenosine

Adenosine, now commonly used as the initial drug treatment for acute narrow-complex tachycardia (PSVT), successfully terminates more than 90% of PSVT.[92,93] Adenosine depresses SA node automaticity and slows AV nodal conduction time and refractoriness. It terminates PSVT of the reciprocating type and nodal reentrant type (including those associated with accessory bypass tracts). It is an effective alternative to verapamil. If adenosine results in SVT conversion, monitoring for recurrence and treatment with adenosine should follow. The rate can be controlled with a longer-acting AV nodal blocking agent (e.g. diltiazem or beta-blocker). Adenosine also provides a valuable new approach to the management of wide-complex tachycardia of uncertain cause, as it unmasks atrial activity allowing the diagnosis of atrial flutter and intra-atrial tachycardia. It has no effect on ventricular tachycardia or preexcited tachycardia.[92]

Adenosine is safe and effective in pregnancy.[94] Its use in pregnancy was first described in 1991[95] with several more cases reported since.[29,57,96,97,98] Adenosine crosses the placenta, but the rapid onset (<1 min) and short half-life (<10 s) following intravenous use minimize the potential for fetal effects.[99,100] A fetus is more likely to be affected by a maternal dysrhythmia than by adenosine itself, because of its short half-life. Larger doses may be required for patients with a significant blood level of theophylline or caffeine. The initial dose should be decreased to 3 mg in women taking dipyridamole or carbamazepine, those with transplanted hearts, or if given by central venous access.

Commonly reported adverse maternal effects include facial flushing, headache, sweating, dyspnea, and chest pain. Symptoms associated with transient asystole may be distressing. Hemodynamically unstable proarrhythmia requiring electrical cardioversion and procainamide have been reported after standard doses of adenosine in the setting of ventricular preexcitation (WPW syndrome).[90,91]

If SVT does not convert with adenosine (6 or 12 mg i.v.) rate control may be achieved using a longer acting AV nodal blocking agent (e.g. verapamil or diltiazem) or a beta-blocker (Class IIa) as a second-line agent.

Verapamil

Verapamil should be given only to patients with narrow-complex reentry SVT, or dysrhythmias known with certainty to be of supraventricular origin. Verapamil should not be given to patients with

Table 2.19 Antidysrhythmic drugs in pregnancy and lactation[38]

Drug	VW classification	FDA classification	Indication	Adverse effects & cautions	Breastfeeding[38]
Adenosine	V	C_M	Supraventricular tachycardias	Facial flushing, transient dyspnea, chest discomfort, hypotension, bronchoconstriction in asthma	No human data Probably compatible
Amiodarone	III (K^+ channel blocker)	D_M	Reentrant dysrhythmias Refractory VT /VF AF/flutter	Bradycardia, prolonged QT, Torsade de Pointes, paresthesia, IUGR, thyroid disorders in mother/neonate	Contraindicated
Digoxin	V	C_M	PSVT, rate control in chronic AF/flutter	Caution in WPW	Compatible
Lidocaine	Ib (Na^+ channel blocker)	B_M	VT, symptomatic PVD, prevention of VF	Drowsiness, agitation, paresthesia, cardiac depression, bradycardia, asystole	Limited human data Probably compatible
Procainamide	Ia (block fast sodium channel)	C_M	SVT, VT, symptomatic PVD, Prevention of VF, AF in WPW (with AV blocking agent), wide complex hemodynamically stable tachycardias	GI symptoms Heart block Torsade de Pointes Lupus-like syndrome	Limited human data Probably compatible
Esmolol Propranolol	II (Beta-blockers)	C_M	Atrial and ventricular tachydysrhythmias Rate control in chronic AF/flutter	Caution: congestive heart failure, asthma Bradycardia: mother/fetus Hypoglycemia: mother/fetus	Limited human data Probably compatible
Quinidine	Ia	C_M	AF/flutter Ventricular tachydysrhythmias	GI symptoms, neonatal thrombocytopenia, heart block, Torsade de Pointes, Lupus-like syndrome	Limited human data Probably compatible
Verapamil	IV Calcium channel blockers	C_M	SVT Slow ventricular rate in AF/flutter	If wide QRS, CONTRAINDICATED until VT ruled out Heart block, hypotension, asystole	Limited human data Probably compatible

VW = Vaughan Williams classification of cardiac drugs; FDA = Food and Drug Administration; $_M$ = added if rated in manufacturer's professional literature; PSVT = paroxysmal supraventricular tachycardia; WPW = Wolff–Parkinson–White syndrome; AF = atrial fibrillation; SVT = supraventricular tachycardia; VT = ventricular tachycardia; VF = ventricular fibrillation; PVD = premature ventricular depolarization

For additional reading about the impact of drugs on pregnancy and lactation the editors recommend:

Briggs, G. G., Freeman, R. K. & Yaffe, S. J. *Drugs in Pregnancy and Lactation*, 6th edn., Baltimore: Williams and Wilkins, 2002.

Hale, T. W. *Medications and Mothers' Milk*, 10th edn., Amarillo, Texas: Pharmasoft Publishing, 2004 (online orders – www.iBreastfeeding.com).

impaired ventricular function or heart failure. Verapamil should be given in a 2.5 to 5 mg i.v. bolus over two minutes. Repeated doses of 5–10 mg can be given 15 to 30 minutes apart to a total dose of 20 mg or a 5 mg bolus q 15 minutes to a total dose of 30 mg.

Diltiazem

The dose of diltiazem is 15–20 mg (0.25 mg/kg) i.v. over two minutes; then 20–25 mg (0.35 mg/kg) in 15 min as required. The maintenance infusion dose is 5–15 mg/h, titrated to HR.

Other uncommon cardiac conditions during pregnancy

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Arrhythmogenic right ventricular cardiomyopathy is a disorder that predominantly affects the right side of the heart and causes ventricular dysrhythmias.[101,102] In many patients the disease is familial and ARVC may account for up to 5% of unexpected sudden deaths. One report described the use of an ICD in a woman with ARVC at 21 weeks' gestation. This life-preserving treatment was associated with a normal remainder of the pregnancy and an uneventful forceps delivery.[101] Another case described the successful use of an epidural anesthetic for labor and C/S in a woman with ARVC and indwelling ICD.[103]

Postural orthostatic tachycardia syndrome (POTS)

Postural orthostatic tachycardia syndrome encompasses a group of disorders characterized by orthostatic intolerance. In one case a parturient had worsening symptoms during pregnancy, which were managed by increasing the dose of beta-blockers. A labor epidural was used successfully and optimal postpartum analgesia was ensured by using neuraxial opioids, NSAIDs, and bilateral iliohypogastric and ilioinguinal nerve blocks. The aim was to reduce the risk of triggering a tachycardic response to the stress of labor and pain.[104]

Cardiopulmonary resuscitation of the parturient

This topic is well covered in ACLS protocols as a separate section.[105] The standard algorithms are applicable to the pregnant woman, including the use of defibrillation. However, because of the physiological changes of pregnancy there are some important principles to remember.

- The parturient will undergo oxygen desaturation more rapidly so supplemental oxygen is required.
- Successful resuscitation of the mother usually results in a better outcome for the fetus.
- There is a higher risk of pulmonary aspiration of gastric contents, so the maternal airway should be protected early with an endotracheal tube. As airway edema is common in the pregnant woman a smaller endotracheal tube may be required.
- Chest compressions should be performed higher on the sternum as the gravid uterus will displace the diaphragm higher in the chest.
- After 20 weeks' gestation, the uterus becomes an abdominal organ. As such it can compress the aorta and vena cava inhibiting venous return to the heart. This will affect cardiac output limiting the ability to resuscitate the pregnant female. Therefore left uterine displacement should be provided by a wedge under the right hip or by manually displacing the uterus to the woman's left.
- If resuscitative efforts are not successful after four minutes the fetus should be delivered by C/S in order to relieve aortocaval compression. This may allow successful maternal resuscitation.
- In addition to the usual causes of cardiac arrest, the following are more common in pregnancy than in the general population: embolic events (thrombotic, amniotic fluid, or air), an overdose of magnesium sulfate, acute coronary syndrome, preeclampsia/eclampsia, and aortic dissection.

Summary

In women with heart disease, sustained dysrhythmias can result in an increased risk to the mother and fetus. Women with preexisting cardiac rhythm disorders are likely to have an exacerbation of dysrhythmia during pregnancy, which increases the risk of adverse fetal complications.[35] Women with congenital heart disease, especially those with subpulmonary ventricular systolic dysfunction and/or severe pulmonary regurgitation, may develop sustained dysrhythmias during pregnancy (3% risk in one study).[32]

The treatment of the pregnant patient with cardiac dysrhythmias may require important modifications of standard dysrhythmia management. The goal is to protect the mother and her fetus through delivery, after which chronic or definitive therapy can be administered.[106] New advances, such as ICD, allow immediate treatment of dangerous heart rhythms, and *fetal magnetocardiography* is a valuable new tool for rhythm diagnosis and for monitoring maternal and fetal rhythms during therapy.[107]

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3 VASCULAR DISEASES

David R. Gambling

Introduction

Maternal vascular lesions that become apparent during pregnancy may be present before conception but only become symptomatic as a result of the physiologic changes of pregnancy. Blood vessels are weakened by an increase in blood volume and cardiac output (CO); a decrease in systemic vascular resistance (SVR); and hormonal changes. Hence, aneurysms can expand and rupture, or arteriovenous (AV) malformations can grow and, if present in the pulmonary circulation, can worsen a preexisting shunt. Some of the rare conditions described in this chapter affect blood vessels in discrete areas of the body whereas others affect all blood vessels. Often the disorders described are part of an autoimmune disease process that impacts other organ systems. Many of the vascular disorders are associated with high maternal and neonatal mortality. For example, rupture of an enlarging aneurysm can cause abrupt, catastrophic blood loss and poor peripartum outcomes. Likewise, pulmonary hypertension worsens during pregnancy and is often associated with maternal and/or neonatal death. This chapter discusses the clinical implications for the obstetric anesthesiologist of most vascular lesions seen during pregnancy. Intracranial aneurysms during pregnancy are discussed in Chapter 9.

Primary pulmonary hypertension

Primary pulmonary hypertension is a progressive disease that produces a sustained rise of at least 25 mmHg in mean pulmonary artery pressure and an increase in pulmonary resistance, in the absence of an identified pulmonary or cardiac lesion.[1,2] This inevitably leads to right ventricular (RV) dilatation and RV hypertrophy progressing to RV failure and death.[1,3] The course of primary pulmonary hypertension usually is slow, but unrelenting, with death occurring 4–6 years after the initial diagnosis. However, its course may be as short as six months from first symptoms to death. This condition is covered in other major textbooks of obstetric anesthesia[4,5] and the following represents a brief outline of the importance of primary pulmonary hypertension to the obstetric anesthesiologist. Discussion of the management of women with Eisenmenger syndrome (pulmonary hypertension secondary to a chronic, uncorrected left-to-right cardiac shunt) is found in Chapter 1.

Primary pulmonary hypertension affects women four to five times more often than men. It may arise at any age, but is most prevalent in the third and fourth decades[6] with a mean age of 27 years at diagnosis.[7] Among the prognostic indicators of survival, the most powerful and easily obtainable is the systemic arterial oxygen saturation (SaO_2). When SaO_2 is greater than 63%, three-year survival is 55%. When SaO_2 is less than 63%, three-year survival is only 17%.[7] Sudden death in primary pulmonary hypertension may be caused by tachycardia and loss of effective atrial systole, acute pulmonary embolism from deep venous thromboses, or from RV ischemia or infarction.[3] A rapid increase in venous return to the right heart, and subsequently to the lungs, may produce a vagally-mediated bradycardia and fall in CO, which can be lethal.[8]

In most cases, postmortem microscopic examination of the lungs reveals that both lungs are affected by diffuse pulmonary vascular changes characterized by intimal proliferation, medial hypertrophy, and perivascular lymphocytic cuffing, described as plexogenic arteriopathy.[9] Others have reported that thrombotic pulmonary arteriopathy is a more likely cause of pulmonary hypertension.[7] Primary pulmonary hypertension caused by pulmonary veno-occlusive disease with intimal proliferation and fibrosis of intrapulmonary veins and venules occurs less frequently.[3]

Signs and symptoms

The signs and symptoms of primary pulmonary hypertension relate to RV compromise and failure. Dyspnea is caused by decreased CO and ventilation/perfusion mismatch. Syncope is due to a fixed CO with the inability of the heart to respond to a demand for increased output. Angina is common, and probably results from RV ischemia and increased RV afterload. Other signs and symptoms include fatigue, edema, and peripheral cyanosis. Occasionally hoarseness may develop due to the pressure of an enlarging pulmonary artery on the recurrent laryngeal nerve, which is known as Ortner syndrome.[3]

During physical examination of the parturient with pulmonary hypertension, a RV heave may be present and an ejection click may be heard over the pulmonic area. The second heart sound usually is split, with accentuation of the pulmonic component. There may be an ejection murmur and a regurgitant murmur over the pulmonary valve. Jugular venous distension and prominent A waves usually are evident. Chest radiography (CXR) demonstrates RV enlargement, hilar enlargement, and pruning of the peripheral vasculature. Electrocardiogram shows RV hypertrophy, and right-axis deviation (see Figure 3.1). Pulmonary function tests may indicate restrictive disease due to decreased lung compliance resulting from elevated pulmonary vascular pressure.[3]

Association with pregnancy

Among women of reproductive age, approximately 8% of primary pulmonary hypertension is associated with pregnancy.[9] It is

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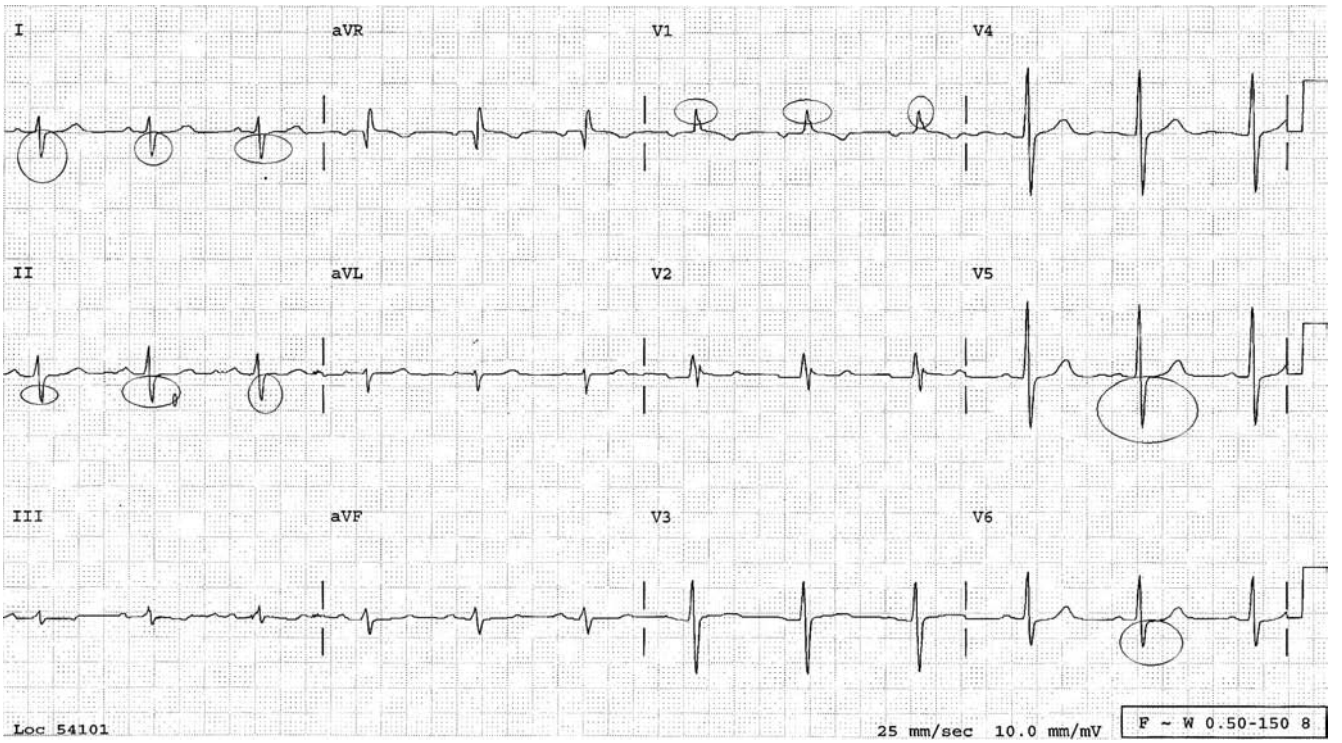

Figure 3.1 EKG from a patient with severe pulmonary hypertension. Note the deep S waves in leads I, II, V5, and V6 plus a prominent R wave in V1 (all circled). Provided by Dr Renaldo Beyer, Cardiologist, Sharp Rees-Stealy Medical Group, San Diego, California.

possible that pregnancy initiates primary pulmonary hypertension in some women, but more likely symptoms of preexisting disease are unmasked by the increased hemodynamic stress of pregnancy.[9] When symptoms arise during pregnancy, the diagnosis is made only after excluding other causes of pulmonary hypertension. These include amniotic fluid embolism, trophoblastic embolism, thromboembolism, obliterative hypertension, and Eisenmenger syndrome.[9]

Primary pulmonary hypertension and pregnancy is an ominous combination. Maternal mortality ranges from 30–56%[1,7,10] with death often occurring during delivery, or from four days to five weeks following delivery despite intensive postoperative management.[11] Death usually is sudden, precipitated by acute RV failure. Absolute pulmonary artery pressure is a poor indicator of the extent of the disease. However, a poor prognosis in pregnancy is associated with the presence of RV hypertrophy, low cardiac index (2–2.5 l/min/m^2), increased right atrial pressure (>10 mmHg) and high pulmonary vascular resistance (>1500 dynes.sec.cm^{-5}).[1] Other maternal risk factors include late diagnosis and late hospital admission.[11] Neonatal survival was reported as 88% in one series.[11]

Treatment of primary pulmonary hypertension

A number of therapies have been tried to treat primary pulmonary hypertension. These include calcium channel blockers and anticoagulation, prostacyclin, and, ultimately, lung transplantation.[12] More recently, the successful use of the endothelin antagonist, bosentan (Tracleer®), has been described in the treatment of pulmonary arterial hypertension.[13] However, bosentan is not approved for use during pregnancy. Perioperative therapies used during pregnancy have included nitroglycerin infusion,[14] inhaled nitric oxide (which is very expensive),[15] or inhaled or intravenous (i.v.) epoprostenol (prostacyclin).[16,17,18]

Anesthetic management of women with primary pulmonary hypertension

The principal goals of anesthetic management of primary pulmonary hypertension include avoiding increases in pulmonary vascular resistance and pulmonary artery pressure, preventing changes in RV preload, and maintaining left ventricular afterload and RV contractility.[19,20] Potent titratable drugs should be readily available in the event of hemodynamic instability. The need for inotropes (dopamine or dobutamine), pressors (phenylephrine or ephedrine), or afterload reducers (nitroprusside or phentolamine) during labor and delivery or cesarean section (C/S) should be anticipated. In one report, a vasopressin infusion was used to prevent systemic hypotension in a patient with primary pulmonary hypertension having surgery under spinal anesthesia.[21]

Prior to the onset of labor, the severity of pulmonary hypertension can be assessed by pulmonary artery catheterization, which also allows an assessment of the response of the pulmonary vasculature to vasoactive drugs.[19,22] Preoperative adenosine and nifedipine have been shown to reduce pulmonary vascular pressure[23] and may be useful adjuncts to oxygen therapy at the time of parturition. It is important to measure right- and left-sided pressures continuously during labor and delivery. However, multiple

pulmonary capillary wedge pressure (PCWP) measurements should be discouraged because of the risk of pulmonary artery rupture.

During delivery an increase in pulmonary vascular resistance can occur as a result of hypercarbia, acidosis, hypoxia, stress, and pain.[22] Epidural analgesia provides excellent pain control and attenuates many of these adverse effects. Investigators have reported successful management of labor and C/S using various doses of epidural local anesthetics, with and without fentanyl.[1,8,22,24,25,26,27,28] The addition of fentanyl to labor epidural infusions is a theoretical concern because of the potential to cause myocardial depression in patients with compromised hearts.[29] However, it is unlikely that 2 μg/ml fentanyl at 10–15 ml/h would produce serum levels that would be clinically important in this regard. Care should be taken to titrate the level of analgesia to avoid hypotension and a reduction in RV preload. Excellent pain relief has also been obtained in patients with pulmonary hypertension using intrathecal morphine.[30,31] However, unless vaginal delivery is imminent, a neuraxial catheter technique is recommended. Forceps or vacuum extraction is often used to help prevent the untoward hemodynamic effects caused by maternal pushing.

Cesarean section can be performed after careful extension of an epidural block to T4–5. The risk of severe hypotension is minimal as long as provisions to support blood pressure (BP) have been taken. Epidural anesthesia,[32,33] combined spinal–epidural (CSE) anesthesia,[34] and general anesthesia all have been used successfully for C/S[25,35] and tubal ligation[36] in patients with primary pulmonary hypertension. Invasive monitoring was used during these procedures. If epidural anesthesia is used, it is uncertain if one local anesthetic is superior to another, although one report described the successful use of 0.75% ropivacaine in this setting, citing the potential advantage of lower cardiac toxicity.[37] Decoene and colleagues described the successful use of inhaled nitric oxide (iNO) in a woman with primary pulmonary hypertension having C/S under epidural anesthesia.[38] They observed no interaction between epidural anesthesia and the use of iNO. Others have reported the use of inhaled pulmonary vasodilators and epidural anesthesia for C/S in pregnant patients with primary pulmonary hypertension.[39]

Proponents of general anesthesia usually cite the risks of decreased afterload, decreased preload, and acute RV failure that may be precipitated by sympathetic blockade induced by epidural or spinal anesthesia.[35] Supporters of regional anesthesia report that careful titration of the level of the block and the judicious use of vasoactive drugs allow for satisfactory management of anesthesia in these women. In addition, pulmonary hemodynamic changes associated with laryngoscopy,[40] which increase the risk for precipitating right heart failure, are avoided with regional anesthesia.

If general anesthesia is selected, nitrous oxide should be avoided since it can increase pulmonary vascular resistance. Isoflurane is the volatile anesthetic of choice for general anesthesia because it has the least depressant effect on the myocardium. It should be used with an air/oxygen mixture.[36] In labile patients, and/or those with severe disease, we recommend invasive monitoring and a high-dose narcotic "cardiac" anesthetic. One report described the use of general anesthesia and extracorporeal membrane oxygenation support for termination of pregnancy in a woman with primary pulmonary hypertension.[41]

Spinal anesthesia is contraindicated due to the risk of rapid-onset deleterious hemodynamic changes. However, even when general anesthesia is used in the presence of a pulmonary artery catheter, and successful intraoperative control of pulmonary artery pressure is achieved using iNO, nebulized iloprost, and a prostacyclin infusion, a patient can still die in the first few weeks following surgery.[42]

In summary, pregnancy should be discouraged in women with primary pulmonary hypertension and therapeutic abortion should be offered, especially with early clinical deterioration. A multidisciplinary approach to the management of a parturient is important, but mortality is high even with the most modern treatment options.[43]

Pulmonary arteriovenous malformations

Introduction

Pulmonary arteriovenous malformations (PAVM) are rare, thin-walled vascular lesions that may complicate pregnancy because of rapid enlargement or rupture (see Figures 3.2 and 3.3). Most PAVM are congenital but many patients are not diagnosed until the second decade. They usually occur singly and grow slowly. However, they can occur as discrete or multiple lesions, in one or more lobes, and in one or both lungs,[44,45] and many small AVM may be scattered throughout the lungs.[45,46] The mortality rate in patients with untreated PAVM is 11%.[44,47]

Signs and symptoms of pulmonary arteriovenous malformations

The usual symptoms of PAVM are dyspnea, cyanosis, and clubbing, which are caused by hypoxemia due to right-to-left shunt.

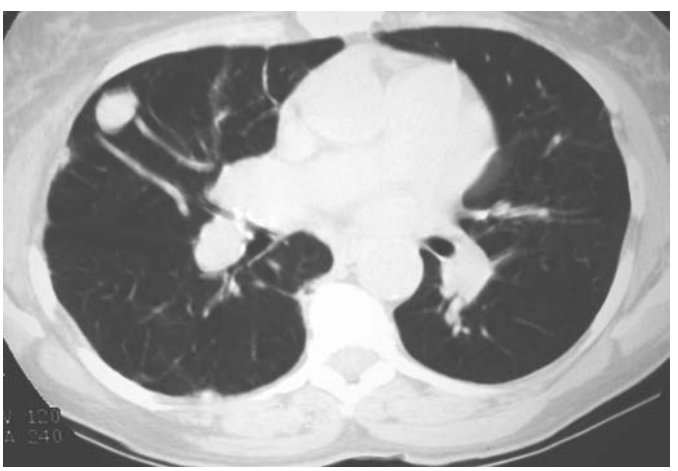

Figure 3.2 CT scan without contrast of right single pulmonary AV malformation (pulmonary artery and vein seen on the same cut). Provided by Dr Frank Miller, Professor of Radiology, University of California San Diego (UCSD) Medical Center, San Diego, California.

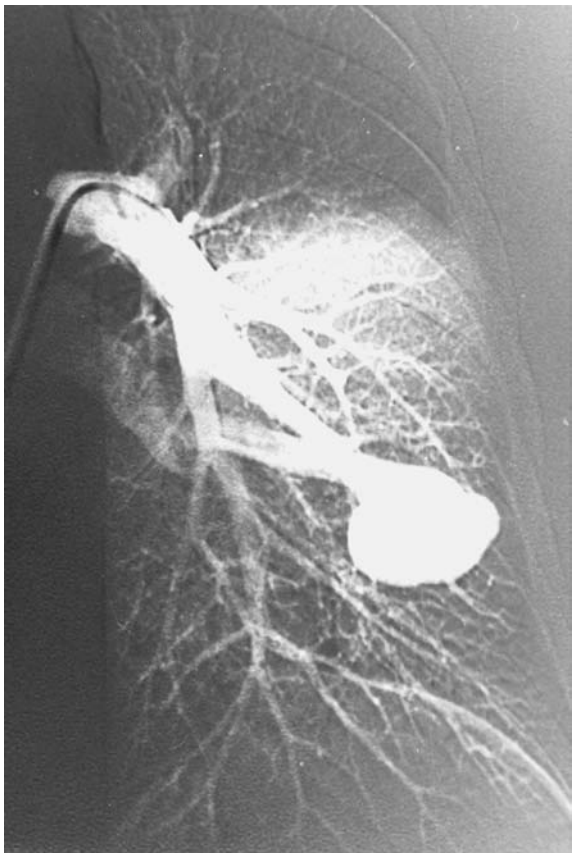

Figure 3.3 Angiogram showing a large left pulmonary AV malformation. Provided by Dr Frank Miller, Professor of Radiology, University of California San Diego (UCSD) Medical Center, San Diego, California.

Hypoxemia induces bone marrow to increase its production of hemoglobin and red blood cells, and may cause polycythemia. A shunt of at least 25% is required to produce clubbing and polycythemia. Although plasma volume remains normal, the red cell mass and red cell volume increase.[44,45] Frequent minor hemorrhages may prevent polycythemia.

Bruits often are audible on the chest wall over an AVM. A continuous hum is accentuated by systole and deep inspiration.[45,48] The characteristic feature on CXR is a peripheral, circumscribed, lobulated, noncalcified structure connected to the hilum by tortuous vessels. Fluoroscopy of the lesion shows pulsations with each heart beat, and increase and decrease in size with Mueller and Valsalva maneuvers (inspiration and expiration against a closed glottis), respectively.

According to Peery, cardiomegaly is "conspicuously absent" in patients with right-to-left shunt.[49] If cardiomegaly is present on CXR, then suspect concomitant right heart disease or a left-to-right shunt. Rib notching occurs when a left-to-right shunt via an enlarged and tortuous intercostal AVM exists.[49] The definitive diagnosis of PAVM is made by angiography.

Complications associated with the pulmonary lesions include vascular shunts, mitral valve disease, congestive heart failure, bacterial endocarditis, hemoptysis, and hemothorax due to rupture. In addition, a cerebrovascular accident (CVA) may occur following cerebral embolism, thrombosis, or abscess.[45,50]

Table 3.1 Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia)

Inheritance: autosomal dominant
Incidence: affects 1 in 5000–8000
Features:
– abnormal small blood vessels
– AV fistulae in most organs, including lung and brain
– telangiectasia of skin and mucous membranes causing epistaxis and GI bleeding
Pregnancy worsens OWR secondary to:
– systemic vascular dilatation
– increased cardiac output
– increased blood volume
– weakened blood vessels from hormonal changes
May present in pregnancy with:
– hemothorax
– massive hemoptysis
– arterial hypoxemia and paradoxical embolism for pulmonary shunts
– congestive cardiac failure from hepatic AV shunts and portal hypertension
– AV fistulae in the epidural space and spinal cord
– anemia

AV = arteriovenous; GI = gastro-intestinal

Most shunts associated with PAVM are right-to-left, but left-to-right shunts of the bronchial, internal mammary, and intercostal arteries have been described.[45] Paradoxical emboli may arise in the systemic circulation and pass through an enlarged and engorged PAVM to affect the cerebral circulation. Likewise, thrombi may originate on diseased valves or within a PAVM, due to the sluggish flow characteristics of AVM, and shower the cerebral circulation. Hemoptysis and hemothorax occur when a lesion ruptures into the airway or pleural cavity, respectively. Paradoxical air emboli can occur when air enters the pulmonary circulation following rupture of a PAVM. Such a rupture is rare, but when it occurs is frequently massive and fatal. Rapid recognition, response, and repair or resection is necessary if the patient is to survive.[48]

Osler-Weber-Rendu disease

About 60% of patients with PAVM suffer from Osler-Weber-Rendu disease (OWR), a disease with autosomal dominant transmission, also called hereditary hemorrhagic telangiectasia (see Table 3.1).[51] About 15% of patients with OWR have PAVM,[52,53] and will frequently exhibit multiple cutaneous and mucous membrane AVM, visible on the lips, labia, and oral mucosa. Epistaxis arising from lesions of the nasal mucosa is highly characteristic.[51] Pregnant women who have a family history of OWR, or have mucocutaneous signs of the disease should be evaluated for the presence of occult pulmonary lesions. Patients with OWR tend to have a high incidence of multiple PAVM, which generally grow more rapidly and produce more complications than in patients without OWR.[46]

Pregnancy and PAVM

Pregnancy increases the risk of PAVM enlargement and rupture.[47,48,52,53,54] The increase in size is a result of the increase in blood volume and CO. Also, hormonal changes of pregnancy directly affect the compliance of blood vessels with an increase in progesterone causing relaxation of arteriolar smooth muscle and further dilatation of the PAVM. Estrogens are associated with the formation of spider telangiectasia and may contribute to an increase in PAVM size during pregnancy.[46] Throughout pregnancy there is a gradual increase in venous distensibility, which is greatest (150% of normal) just before delivery, similar to the 20–30% increase in venous distensibility observed during the menstrual cycle.[55,56,57] The structure of the AVM contributes to its fragility. The vascular spaces are lined by a single layer of endothelial cells on a continuous basement membrane.[58] Smooth muscle cells within the walls of the AVM are irregularly shaped and do not form a continuous structure around the blood vessels. Both endothelial cells and smooth muscle cells are vacuolated, which suggests degeneration. There is no elastic tissue within the walls. Thus, the walls of an AVM appear to be insufficient as a contractile element and are unable to respond to the increased stress associated with the increased blood volume and CO of pregnancy.[58] The walls of an AVM, therefore, cannot contract and control hemorrhage when they rupture.[48,58] In addition, there may be an increase in tissue plasminogen activator in the endothelium of AVM, which impairs clot formation when bleeding occurs.[59]

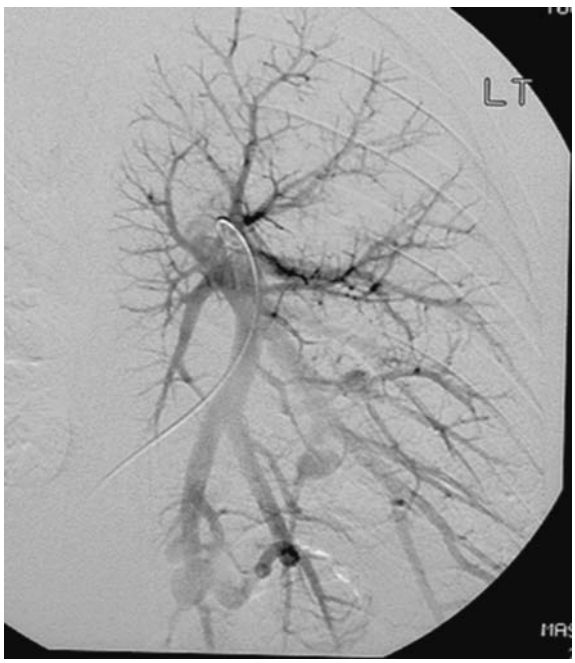

Figure 3.4 Angiogram of multiple AV malformations in a woman with Osler-Weber-Rendu disease. She was 24 weeks' gestation (preembolization), with a history of transient ischemic attacks and SaO_2 in 85–88% range. Provided by Dr Frank Miller, Professor of Radiology, University of California San Diego (UCSD) Medical Center, San Diego, California.

Management of the pregnant patient with PAVM

When PAVM become symptomatic during pregnancy, they can be managed successfully using transcatheter spring coil or balloon embolization.[60,61] These procedures are done under local anesthesia and successful occlusion will usually resolve the hypoxemia and high-output cardiac failure (see Figures 3.4, 3.5, and 3.6). However, there has been a case report of recurrence of PAVM in pregnancy despite previous transcatheter embolotherapy.[62] This was discovered by contrast echocardiography after the woman developed signs of worsening intrapulmonary shunt.

When multiple lesions exist they may not be amenable to embolization, so pulmonary lobule or lobe resection may be necessary to eliminate them. This surgery is most safely performed during

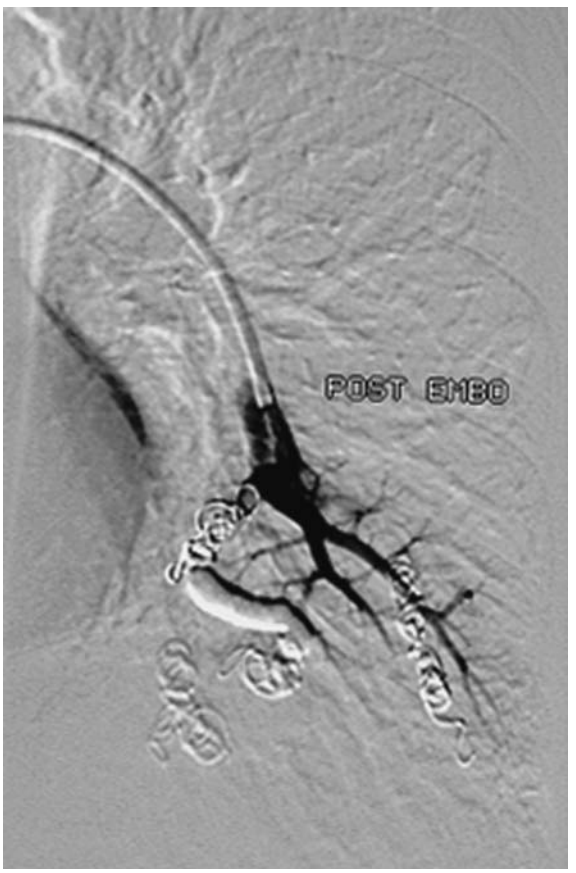

Figure 3.5 Same pregnant women postembolization with SaO_2 93%. (Multiple AVM prevent saturation from reaching 100%.) Provided by Dr Frank Miller, Professor of Radiology, University of California San Diego (UCSD) Medical Center, San Diego, California.

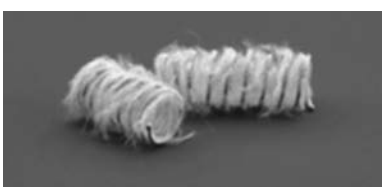

Figure 3.6 Coil used for coil embolization procedure, which is usually done on an outpatient basis (Nester coil™). Provided by Dr Frank Miller, Professor of Radiology, University of California San Diego (UCSD) Medical Center, San Diego, California.

the second trimester to avoid the period of fetal organogenesis and to reduce the risk of preterm labor. One case report described an emergency thoracotomy at 27 weeks' gestation for massive hemothorax associated with a pulmonary arteriovenous fistula in a patient with OWR.[63]

Women with known PAVM or history of hereditary telangiectasia should be followed with serial CXR and arterial blood gases to detect progression of the PAVM.[64] Antenatal diagnosis and treatment of women with OWR and PAVM may prevent potentially life-threatening fetomaternal complications.[65] However, one patient, with exercise-induced hypoxemia during pregnancy related to pulmonary AV microfistulas, had spontaneous resolution of her symptoms after pregnancy. This was thought to be due to reversal of the hormone-induced vasodilatation associated with pregnancy.[66]

Anesthetic management of women with PAVM

There are few case studies to guide us when it comes to recommending certain anesthetic and analgesic techniques for labor and delivery in women with PAVM. However, I believe that epidural analgesia is acceptable. Placement is performed using loss of resistance to saline to avoid the risk of introducing air into the vascular system and the risk of paradoxical air emboli. Since there may be coexisting epidural AVM, a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the lumbar spine in the early third trimester may be prudent. After delivery and epidural catheter removal, the woman should be followed for signs of epidural hematoma, presenting as persistent paresthesia, pain, or paralysis after expected resolution of analgesia.

The epidural sensory level should be carefully titrated to a T10 dermatomal level in order to avoid a significant reduction in SVR and worsening of right-to-left shunt. If required, SVR support may be provided with a phenylephrine drip while monitoring the fetal heart rate. Arterial and pulmonary artery pressure monitoring is necessary when heart failure is suspected, but PCWP measurement may be hazardous due to the risk of PAVM rupture. An arterial line also is necessary when infusing vasoactive drugs to increase SVR.

Cesarean section may be performed for obstetric reasons using regional or general anesthesia. The latter has the potential disadvantage of intubation-induced hypertension and the possibility that high pulmonary inflation pressures might adversely impact the integrity of the AVM. One case report of the anesthetic management of a child with OWR and bilateral PAVM described the association between positive pressure ventilation and arterial desaturation, which improved with resumption of spontaneous respiration after extubation.[67] That case was confounded by coexisting congenital methemoglobinemia, another potential cause of cyanosis in that patient.

Arteriovenous malformations of the oral, pharyngeal, or tracheal mucosa may exist. Therefore, thoroughly examine the upper airway when considering general anesthesia and endotracheal intubation in these patients to avoid inadvertent trauma to the mucosal lesions.

Since OWR is sometimes associated with liver AVM and liver dysfunction, it is prudent to do an ultrasound of the liver in these patients and to check the coagulation status. Liver involvement can lead to high-output cardiac failure in patients with OWR, but cardiac function may return to normal after liver transplantation.[68]

Another association with PAVM is the risk of brain abscess and cerebral AVM.[69,70] One large series described neurologic complications in 37% of patients with PAVM and these included transient ischemic attacks, hemiplegia, brain abscess, and seizures. Any patient with OWR presenting for an anesthetic must have neurologic dysfunction ruled out by history, physical examination, and special tests such as a brain scan. Patients with PAVM require prophylactic antibiotics for all surgical and dental procedures to avoid brain abscess or other distal infectious complications.

Dyspnea may improve when the patient reclines. In the supine position, there is decreased venous return due to the pressure of the gravid uterus on the vena cava, decreased distension of the PAVM, and decreased shunt. Hemoglobin saturation improves. Thus, it may be beneficial for the patient with a symptomatic PAVM to labor without uterine displacement. We recommend that if this is attempted, the well-being of the fetus be monitored. Postpartum it is imperative that these patients be monitored carefully for any deterioration as the effect of the gravid uterus on venous return is abolished and autotransfusion of blood from within the gravid uterus increases venous return and shunt. It may be necessary to resect or embolize the PAVM if the shunt increases significantly.

Finally, it is important to consult surgical colleagues and perinatologists early in the pregnancy of a patient with OWR. Delivery should be planned in a hospital with resources available to place chest drains if necessary, a well-stocked blood bank, and an intensive care unit.

Peripheral pulmonary artery stenosis

Peripheral pulmonary artery stenosis (PPAS) is a rare congenital condition of unknown etiology, which accounts for 2–4% of congenital heart disease in women. It is characterized by multiple coarctations of the distal pulmonary arteries.[71] Peripheral pulmonary artery stenosis may occur together with pulmonary stenosis, atrial septal defect, ventricular septal defect, or Tetralogy of Fallot. This condition occurs alone in approximately 40% of cases.[72] There may be an association of PPAS in offspring of women who contract rubella during pregnancy.[73]

Peripheral pulmonary artery stenosis is not usually considered a serious condition. Often it is diagnosed in early childhood when a loud, asymptomatic, continuous systolic murmur is investigated. Only when involvement of the peripheral pulmonary arteries is so extensive that it produces pulmonary hypertension is there a risk to the patient. Such a development is uncommon.[71]

Four cases of PPAS and pregnancy have been reported.[71,72,73] In none of the cases did PPAS present a management problem for the anesthesiologist. During pregnancy, echocardiography or cardiac catheterization should be performed to detect elevated right heart pressures and assess the relative risk for heart failure during or after pregnancy. If the woman has pulmonary

Table 3.2 Pulmonary artery aneurysms and pregnancy

Associated conditions
- patent ductus arteriosus
- Marfan syndrome (cystic medial necrosis of the pulmonary artery)
- Takayasu arteritis
- persistent pulmonary artery hypertension (primary or associated with congenital cardiac defects that produce left-to-right shunting)
- infundibular stenosis
- infective endocarditis

Factors that may contribute to aneurysm formation and rupture
- atherosclerosis
- trauma
- syphilis
- pregnancy
  - an increase in intravascular volume
  - the pain and expulsive efforts of labor
  - involution of the uterus postpartum produces increased flow through the pulmonary arteries and raises vessel wall stress
  - increased deposition of mucopolysaccharides in the media of major blood vessels occurs during pregnancy and may contribute to weakening of the artery

hypertension, she should be managed as described for the patient who has primary pulmonary hypertension (see earlier). If right heart pressures are normal, or only mildly elevated, she requires no special management.

Pulmonary artery aneurysm

Incidence and clinical presentations

Pulmonary artery aneurysms occur rarely and affect the main pulmonary artery or a major branch of the pulmonary vascular tree. Their incidence is approximately 1:10 000 to 1:20 000 of the general population.[74] Associated conditions and contributory factors are outlined in Table 3.2.[74,75]

Rupture of aneurysms of the pulmonary arteries may produce massive and fatal hemoptysis. Death may also be caused by cardiac tamponade if a pulmonary artery ruptures into the pericardial sac.[74,75] One report described a woman in the sixth month of pregnancy with a massive hemothorax secondary to a ruptured lingular artery aneurysm.[76] Another report described a pregnant woman with a pulmonary artery aneurysm that the authors believed represented a case of primary pregnancy-related pulmonary artery aneurysm, since they could find no other predisposing factors.[77] The reasons that there is an increased risk of aneurysm formation and rupture during pregnancy are outlined in Table 3.2.[78]

Signs and symptoms

A pulmonary artery aneurysm may cause shunting and cardiac failure. The patients present with exertional dyspnea, cough, hemoptysis, chest tightness, and possibly hemothorax.[74,75,76,77]

Table 3.3 Heart sounds and murmurs that may be heard in patients with pulmonary artery aneurysms

- Those consistent with **patent ductus arteriosus** (e.g. a to-and-fro murmur heard best at the left second intercostal space, a midsystolic hyperdynamic flow murmur of the mitral valve, and paradoxical splitting of S2)
- **Intracardiac shunts** (i.e. usually fixed, wide split S2, and murmur of increased pulmonic flow)
- **Pulmonary hypertension** (i.e. tricuspid regurgitation characterized by a holosystolic murmur, which increases with respiration, or pulmonic and aortic regurgitation characterized by decrescendo diastolic murmurs)

The heart sounds and murmurs that might be heard on clinical examination are listed in Table 3.3.

Chest radiographs may show pulmonary artery enlargement, cardiac hypertrophy, and decreased peripheral vascular markings characteristic of pulmonary edema. The definitive diagnosis of a pulmonary artery aneurysm and its dissection, however, is based on angiography, CT, or MRI. The EKG will usually show right-axis deviation due to RV hypertrophy.

Anesthetic management during pregnancy

Pulmonary artery aneurysm and dissection almost invariably are associated with pulmonary hypertension,[78] so the anesthetic management is similar to that for primary pulmonary hypertension. The presence of a pulmonary artery aneurysm is life-threatening but, as it occurs rarely, there is no consensus about management. The options are predelivery repair, selective coil embolization,[76] or expectant management of pregnancy, labor, and delivery without repair.

During labor, the goal should be to minimize hemodynamic stresses such as systemic hypertension or profound swings in preload and afterload. This is best achieved with a labor epidural using an infusion of dilute bupivacaine and/or intrathecal opioids. Epidural analgesia is induced gradually to a level of T10 to abolish the pain of labor and delivery, and prevent a catecholamine-induced rise in CO and pulmonary artery pressure. Forceps or vacuum delivery helps to shorten the second stage of labor and avoids the need for expulsive effort by the parturient. As in patients with primary pulmonary hypertension, peripheral arterial, central venous, and pulmonary artery catheters can provide useful information and are mandatory if rapidly titratable vasoactive medications are given to optimize cardiovascular function.

The principles for managing C/S in these patients are the same as for patients with pulmonary hypertension and Marfan syndrome (see later). Carefully titrated epidural anesthesia is preferable to subarachnoid block (spinal anesthesia) because the degree and acuity of hemodynamic changes are less extreme. Spinal anesthesia for C/S, however, is not absolutely contraindicated.

Takayasu arteritis (occlusive thromboarteropathy)

Introduction

Takayasu arteritis (TA), or occlusive thromboarteropathy, is an idiopathic condition characterized by obliterative panarteritis. Symptoms are related to the organ systems involved by stenosis and obliteration of large and intermediate arteries.[79] This chronic inflammatory disease can affect any artery, but significant signs and symptoms arise from involvement of the aorta, its major branches, and the pulmonary arteries.[80] Upper extremity involvement has led to the name *pulseless disease*. Inflammation and subsequent fibrosis affect the arterial media, intima, and adventitia, with intimal involvement being the direct cause of arterial stenosis and obliteration.[80,81] The characteristic pathologic change observed in affected vessels is fibrosis. Signs and symptoms of TA reflect the vascular beds and organs to which blood flow has been diminished.

Takayasu disease affects women almost six times as often as men[79,82] and it affects Asian and Hispanic women predominantly.[83] Although the onset of the disease occurs between the ages of 11 and 48 years,[84] it arises predominantly during the second and third decades of life;[83] therefore, pregnancy can be a coexisting condition.

Classification and prognosis

Several classifications of TA have been proposed with some based on the site of the anatomic lesions and others based on the natural history and prognosis of the disease.[80,85,86] Takayasu arteritis can be a severe and life-threatening disease, especially with more extensive vessel involvement, such as the descending aorta, carotid, and vertebral arteries. Takayasu arteritis is also classified as severe if there is retinopathy, hypertension resistant to treatment, aortic regurgitation, and presence of aneurysms, especially in the pulmonary circulation.[87] Hypertension is severe if the systolic brachial artery pressure is $\geq$200 mmHg and/or the diastolic pressure is $\geq$110 mmHg; or the popliteal systolic pressure is $\geq$230 mmHg and/or the diastolic pressure is $\geq$110 mmHg.[86] Hypertension is most often associated with renal artery stenosis.[88] Takayasu arteritis is a chronic disease with survival of up to 14 years after onset, and periods of remission are common.[89] Early treatment with steroids, cytotoxic agents, and anticoagulants can slow progression of the disease and its consequences. Despite ongoing treatment, the five-year mortality rate for high-risk patients can be as high as 30%. In one series, treatment failed to induce a remission in 25% patients with TA, and half of those who achieved remission later relapsed.[88] Patients with less severe forms of TA do significantly better, with only one death in another series of 31 patients with mild TA.[86] Morbidity is caused by severe uncontrolled hypertension with end-organ dysfunction (e.g. renal insufficiency) and stenosis of major blood vessels affecting regional circulation. Death can result from congestive heart failure or CVA.

Takayasu arteritis and pregnancy

Pregnancy in patients with early TA is not associated with an increased risk for obstetric complications.[90] One case report described a woman with TA who survived three pregnancies during a four-year follow-up period with no serious complication.[91] If TA is symptomatic, 50% of pregnant patients will require management of hypertension. Takayasu arteritis is not associated with an increased rate of premature labor, but intrauterine growth restriction is seen often in the fetus. Neonatal outcome is worse with abdominal aortic involvement, with severe hypertension during pregnancy (especially in the presence of preeclampsia), and with delayed management of TA.[92] Induction of labor and C/S are performed for the usual obstetric indications.[90]

Some patients with TA have resolution or improvement of their symptoms during pregnancy,[93] whereas others demonstrate either no change or worsening symptoms.[94] One woman presented with massive hemoptysis during pregnancy.[95]

The risk of cerebral ischemia is increased during pregnancy especially during the first trimester and early postpartum period. A small reduction in mean arterial BP in patients with severe occlusive disease has the potential for syncope or severe cerebral ischemia.[94] Cerebrovascular accidents are likely when patients have severe narrowing of the branches of the aortic arch, elevated systolic BP during the first stage of labor, and complications of TA such as carotid disease or retinopathy.

Avoiding pregnancy or elective termination of pregnancy is recommended for patients with severe disease.[94] The recommendation for women who decline termination of pregnancy is hospitalization and symptomatic management. Elective C/S may be used for women with severe disease as they approach term, especially those with retinopathy and severely elevated BP in early labor. In those with mild TA, operative delivery is based solely on obstetric factors.

Anesthetic management of women with TA

The anesthetic management of women with TA must take into account the susceptibility of the patient to severe hypertension with its concomitant risk of CVA and cardiac failure. Hypotension is poorly tolerated and may result in cerebral ischemia. Other considerations include the risk of pulmonary hypertension, and difficulty of hemodynamic monitoring due to the nature of the disease.

The need for invasive hemodynamic monitoring must be assessed for each patient. Early consultation is desirable to define the arterial involvement, review aortography, assess the cardiovascular status, and control BP.[96,97] Patients with mild disease have little hemodynamic compromise. Electrocardiogram, pulse oximetry, and noninvasive BP monitoring is adequate for these women. When TA affects peripheral arteries, however, noninvasive BP measurements may be inaccurate or unobtainable. In such cases a peripheral arterial catheter should be inserted,[83] but occasionally a central arterial catheter introduced via the femoral artery may be required.[98] The use of such catheters carries a risk of arterial occlusion at the site of insertion.[99,100,101]

When TA is associated with heart failure, it is necessary to monitor central venous, right heart, and pulmonary capillary wedge pressures. Calculation of CO, systemic, and pulmonary

vascular resistance helps to prevent heart failure and maintain adequate cerebral and renal perfusion.[102] For labor and delivery, epidural analgesia has the advantage of providing effective pain relief while preventing acute catecholamine release associated with labor pain. The anesthesiologist should carefully titrate the dose of local anesthetic in order to produce a level satisfactory for delivery without causing severe hypotension, which could lead to cerebral ischemia.[103] Supplemental oxygen, and laboring in the lateral position, help ensure adequate oxygen delivery to the fetus.

Any contemporary epidural technique would be suitable as long as dilute solutions of local anesthetic are used (e.g. $\leq$0.125% bupivacaine) in conjunction with supplemental epidural opioids (e.g. fentanyl). Vasoactive drugs should be readily available to treat potential fluctuations in BP.

For C/S, epidural anesthesia must be induced slowly and incrementally using whatever combination of local anesthetic and opioid you would normally use. It is questionable whether epidural epinephrine should be used in parturients with TA. One advantage of regional anesthesia for C/S is that the patient remains awake. This gives the anesthesiologist a clinical assessment of cerebral perfusion, which central or peripheral arterial pressures may not accurately reflect. Epidural and CSE anesthetics have been described for C/S in women with TA.[104,105] Spinal anesthesia has been successfully used for termination of pregnancy in a woman with TA, but the usual risks related to potential hypotension must be considered before using spinal anesthesia.[99]

General anesthesia can be given for C/S, although evaluation of cerebral perfusion becomes more difficult or impossible, even with an electroencephalogram (EEG). Patients with severe carotid disease, however, should have EEG monitoring to help prevent cerebral ischemia during general anesthesia. One case report described the use of general anesthesia with processed EEG monitoring in a woman with TA and bilateral carotid artery stenosis.[106] She refused regional anesthesia for C/S and the general anesthetic was uneventful.

Pretreatment with beta-adrenergic blockers (e.g. labetalol in 5 mg to 10 mg increments titrated to the desired response), nitroglycerin (50 μg to 100 μg) or lidocaine (1–1.5 mg/kg) i.v. can attenuate the rise in systolic BP that accompanies endotracheal intubation. Rapid sequence induction with thiopental and succinylcholine is performed and the airway secured. During endotracheal intubation, extreme extension of the patient's neck must be avoided because stenosis of the carotid arteries predisposes to occlusion and hence the risk of cerebral ischemia. Nitrous oxide must be avoided if pulmonary vasoconstriction and hypertension are present. Nitrous oxide has been used without adverse reaction in a parturient with TA, but pulmonary hypertension was ruled out before its administration.[107] Oxytocin has been given to provide uterine contraction safely following delivery, but prostaglandin $F_{2\alpha}$ and ergot alkaloids should be used cautiously as they can cause systemic and pulmonary hypertension. For a review of the anesthetic management issues in women with TA, the reader is referred to a case series by Kathirvel *et al.*[108]

Spinal anesthesia in TA is controversial because of an increased risk of hypotension. There is one published article that described the use of spinal anesthesia for C/S in a patient with TA.[108] Preoperative volume expansion with 15–20 ml/kg of a glucose-free crystalloid solution, and judicious use of ephedrine or other pressors are especially important in maintaining BP and vital organ perfusion during spinal anesthesia.[99] Left uterine displacement is even more critical in these patients when regional anesthesia is administered.

Patients with TA frequently receive anticoagulants and corticosteroid therapy. Coagulation abnormalities must be corrected before instituting regional anesthesia in order to avoid an epidural hematoma. Adrenal suppression may be assumed and supplemental perioperative steroids considered.

In summary, Takayasu arteritis presents in women of childbearing age with a variety of signs and symptoms depending on the stage of the disease, its progression, and response to treatment. The impact of pregnancy on the disease is unclear, but worsening ischemic symptoms, cardiac failure, cerebral hemorrhage, and uncontrolled hypertension can occur. Noninvasive technologies, such as MRI, assist in the diagnosis of TA during pregnancy, avoiding angiography until the postpartum period.[109] In addition, interventional radiologists can help improve outcomes by performing percutaneous transluminal angioplasty and wall stents, when indicated.[110]

Marfan syndrome

Incidence and clinical findings

Marfan syndrome (MFS) is a hereditary disorder of connective tissue affecting collagen and elastin. It is a disorder caused by mutations in the gene that encodes fibrillin-1 (FBN-1) located on chromosome 15. More than 500 mutations have been identified and almost all are unique to an affected individual or family.[111] Marfan syndrome is transmitted in an autosomal dominant manner without gender or racial preference. Marfan syndrome occurs in 4–6 of 100 000 births and, although there is often a family history, 15% of cases are thought to arise as new mutations.[112] Genotype–phenotype correlations in MFS have been complicated by the large number of unique mutations reported, as well as by clinical heterogeneity among individuals with the same mutation. Further studies are needed to investigate the role of modulating genes and genotype–phenotype correlations. Long-term follow-up studies may reveal the prognostic significance of aortic elasticity and may identify patients at risk of aortic complications. When one parent has Marfan syndrome, the fetus has a 50% risk of inheriting the mutant gene.[113]

There are a number of clinical manifestations of MFS (see Table 3.4), but the most important is aortic root dilatation, which can lead to dissection and rupture. The defect in the vessel wall is caused by cystic medial necrosis. The ascending aorta is the most frequent site of dissection because it sustains the greatest stress during systole. Aortic elasticity determined by measurement of local distensibility and flow-wave velocity with MRI is decreased in nonoperated patients with Marfan syndrome. Aortic distensibility of the thoracic descending aorta appears to be the strongest predictor for descending aortic complications. Over the

Table 3.4 Clinical features of Marfan syndrome

Eyes	ectopia lentis
	myopia
Skeletal	arachnodactyly
	pectus deformity
	kyphoscoliosis
	high narrow palate
	increased bone length
	cervical spine abnormalities
Pulmonary	Propensity to develop:
	• pneumothorax (4.4%)[a]
	• bullous emphysema
	• restrictive lung disease
Cardiovascular	Cystic medial necrosis of aorta:
	• aortic dilatation
	• aortic dissection and rupture
	• mitral valve prolapse
	• premature coronary artery disease

[a] Ref. Hall, J. R., Pyeritz, R. E., Dudgeon, D. L. & Haller, J. A., Jr. Pneumothorax in the Marfan syndrome: prevalence and therapy. *Ann. Thorac. Surg.* 1984; **37**: 500–504.

past 30 years, improvement of diagnostic modalities and aggressive medical and surgical therapy have resulted in considerable improvement of life expectancy of patients with MFS.[111] Selected manifestations of MFS reflect excessive signaling by the transforming growth factor-beta (TGF-beta) family of cytokines. Aortic aneurysm in a mouse model of MFS is associated with increased TGF-beta signaling and can be prevented by TGF-beta antagonists such as TGF-beta-neutralizing antibody or the angiotensin II type 1 receptor (AT1) blocker, losartan. AT1 antagonism also partially reversed noncardiovascular manifestations of MFS, including impaired alveolar septation. These data suggest that losartan, a drug already in clinical use for hypertension, merits investigation as a therapeutic strategy for patients with MFS and has the potential to prevent the major life-threatening manifestation of this disorder.[114]

Mitral valve prolapse (most frequently of the posterior leaflet), and myxomatous degeneration of the mitral valve occur frequently in MFS. Mitral valve pathology is detectable by echocardiography in at least 68% of these patients.[115] Mitral valve prolapse is suggested by the presence of a systolic click, best heard just medial to the cardiac apex.

Relatively unknown cardiovascular manifestations of Marfan syndrome include dilatation of the main pulmonary artery and early onset coronary artery disease. In a series of 50 patients with Marfan syndrome, MRI showed 74% had an enlarged pulmonary artery root above the upper limit of normal.[111] Early onset of coronary artery disease may occur in patients with MFS, producing a high rate of dysrhythmias and conduction disturbances.[116]

For patients with MFS, aortic dilatation begins early in childhood. Progressive dilatation occurs slowly but at varying rates among individuals. Life-threatening complications of aortic disease are more common after the aortic root dilates to >60 mm. The normal aortic root diameter is about 22 mm. One study indicates that patients who have an aortic root diameter >30 mm should be considered for prophylactic aortic surgery.[117] The aortic root lies in the cardiac shadow on CXR, and thus aortic dilatation can be missed unless echocardiography, CT, or MRI is performed.[114] Patients should have an echocardiogram performed annually to look for changes in the aortic root diameter.

Advances in surgical and medical therapy over the past two to three decades have decreased the mortality of affected individuals. However, significant mortality still occurs, peaking in the third and fourth decades of life. Although surgery usually provides successful treatment of aortic dissection, it is uncertain whether surgical repair confers a mortality advantage.[118] Some authors suggest that patients with MFS and thoracic aortic disease should have elective valve-sparing surgery rather than composite graft, primarily to avoid the complications of anticoagulation.[118] Emergency surgery and a history of aortic complications in first-degree relatives are associated with a higher mortality. Chronic beta-blocker therapy may slow the rate of aortic dilatation and may be associated with a more favorable prognosis.

Pregnancy and Marfan syndrome

Effect of Marfan syndrome on pregnancy outcomes

In a retrospective study of 63 of the 122 enrolled women with MFS,[119] 142 pregnancies were reported, including 111 that reached >20 weeks' gestation, 28 (20%) that miscarried, and three elective abortions. An obstetric and/or neonatal complication occurred in 40% of all completed pregnancies. The most important complication was an increased number of premature deliveries ($n=17$, 15%) mostly due to preterm premature rupture of membranes and cervical incompetence. This contributed to a markedly increased combined fetal and neonatal mortality of 7%. These findings were the same whether the diagnosis of MFS was made prior to conception or after the woman was pregnant.[119]

Effect of pregnancy on Marfan syndrome

During pregnancy, a 30–40% increase in CO by the second trimester results from an equal increase in heart rate and stroke volume.[120,121] During labor this increase is more profound (100% greater than prepregnancy levels), and immediately following delivery the stroke volume may increase a further 40–50% above prepregnancy levels.[122] The high serum estrogen concentration of pregnancy causes connective tissue changes at the subcellular level, which produce collagen "softening". The increased stress placed on the aortic root by increased CO, preexisting cystic medial necrosis, and estrogen effects all contribute to an increased risk for aortic dissection during pregnancy. Half of all aortic dissections in women of childbearing age occur during pregnancy.[122]

Women with known MFS who are pregnant or wish to become pregnant should first be counseled that half of their children will

be affected by the disease. If pregnancy is desired, the parturient should have a thorough cardiovascular assessment including an echocardiogram. At least one study has indicated that women with MFS whose aortic roots are < 40 mm in diameter seldom have serious cardiovascular complications during pregnancy, and so tolerate pregnancy well.[123] Another report has indicated that pregnancy may be safe with aortic root diameters < 45 mm.[124] Those patients whose aortic root diameters > 40 mm should be counseled against becoming pregnant, irrespective of their New York Heart Association (NYHA) functional class.[124] All pregnant women with MFS are considered high risk, and require on-going evaluation, including echocardiograms every six weeks during their pregnancies.[125]

Aortic dissection

Along with hypertension (most common), connective tissue disorders, and Turner syndrome, MFS is a predisposing condition for the development of aortic dissection (see Figures 3.7A and 3.7B). Acute aortic dissection has a fatality rate of 36–72% within 48 hours. Without intervention, 62–91% of patients will die within one week.[126] An aortic dissection is a tear in the intima secondary to blood dissecting along the intima (see Figure 3.2). Dissection causes an intimal flap, which can cause obstruction of the aorta or its branches or serve as a nidus of thrombus generation. Spiral CT, MRI, and transesophageal echocardiography (TEE) are all equally accurate in the diagnosis of aortic dissection.[127] The maximal risk of aortic dissection is in the third trimester of pregnancy. More than 50% of 40-year-old women in whom an arterial aneurysm ruptures sustain the rupture during pregnancy.[128] Stanford Type A dissection involves the aorta proximal to the origin of the left subclavian artery, regardless of distal extent. Stanford Type B is a dissection confined to the descending aorta. Most patients with Type A dissection are treated surgically whereas those with Type B dissections are usually managed medically. Women with MFS and acute Type A aortic dissection are often managed by cesarean delivery and concomitant aortic repair.[129]

In summary, women with MFS are at significant risk of aortic dissection during pregnancy even if there is no cardiovascular abnormality prepregnancy. Aortic root dilatation may be a predictor of risk, but dissection can occur without significant dilatation.[130] In addition, serial echocardiograms may fail to predict aortic dissection during pregnancy in women with MFS.[131]

Anesthetic management of women with Marfan syndrome

If the parturient with MFS does not have signs or symptoms of cardiac failure, and the aortic root diameter is < 40 mm, she does not require special care for labor and delivery.[132] However, antibiotic prophylaxis against bacterial endocarditis should be provided because of the occult collagen changes present in this disorder. Vaginal delivery is permissible for the asymptomatic patient. Anesthetic management focuses on minimizing aortic root shear forces and wall stress through invasive monitoring, pharmacologic intervention, and pain treatment.[120] Epidural analgesia for labor should be initiated early in order to prevent pain-induced catecholamine release, elevated BP, and increased CO. An infusion of i.v. crystalloid solution can be titrated in 250 ml aliquots slowly up to 750 ml, as required. Slow titration of the epidural level to a T10 sensory level will help to prevent a sudden fall in SVR and BP. Avoiding epinephrine-containing solutions risks poorer quality anesthesia and is of uncertain value in these patients. Significant hypotension should be treated with phenylephrine to avoid the beta-agonist effect of ephedrine. One case report described labor epidural analgesia in a woman with MFS.[133] The authors used direct arterial BP monitoring and a double-catheter epidural technique with continuous epidural infusion of a 0.125% bupivacaine and 0.0002% fentanyl solution. The baby was delivered vaginally after almost eight hours using

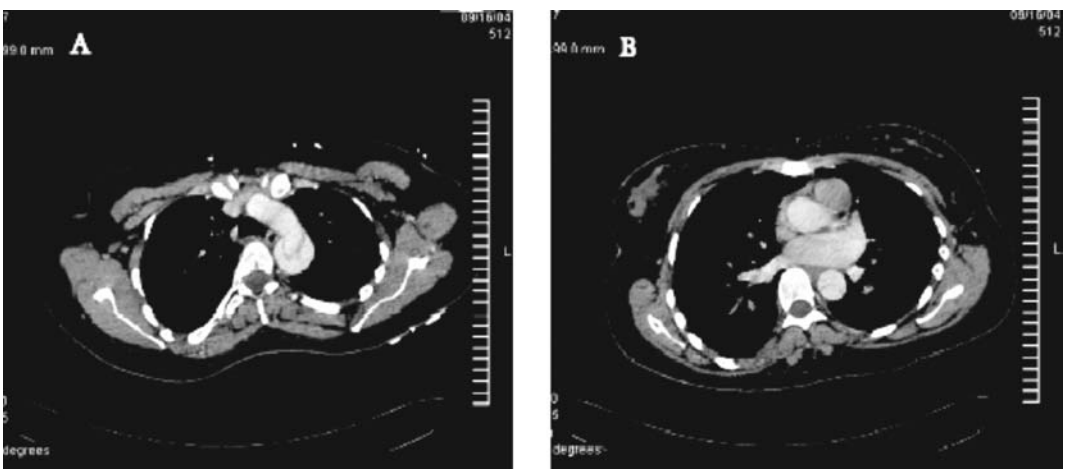

Figure 3.7 (A&B) Aortic dissection in a patient with Marfan syndrome. From: Ioscovich, A. Images in anesthesia: transesophageal echocardiography during Cesarean section in a Marfan syndrome patient with aortic dissection. *Can. J. Anesth*. 2005; **52**: 737–8. (Used with permission of the author and the journal editor.) Figure 3.7A shows the aortic dissection at the level of one section of the descending aorta. Figure 3.7B shows the aortic dissection at the level of the aortic arch. They were both taken at the same time three days prior to the cesarean delivery.

an elective forceps delivery. There were no cardiovascular complications and the patient was discharged from hospital after six days.[133]

In low-risk women with MFS, C/S is indicated only for obstetric reasons. Either regional or general anesthesia can be used for C/S, although regional anesthesia is preferred. The same caveats should be applied to epidural anesthesia for C/S as for labor and vaginal delivery. For general anesthesia, the combined use of beta-blockade and vasodilator therapy will prevent a sudden rise in BP and CO during endotracheal intubation. Volatile agents for these parturients are useful because they decrease cardiac contractility.[116] Positive pressure ventilation must be used carefully to avoid inducing pneumothorax (see Table 3.4).

In women with MFS who are high risk on the basis of cardiac symptoms, an aortic root size >40 mm, significant aortic valve disease, or the presence of aortic dissection, it is even more important to use invasive monitors and vasoactive infusions to minimize abrupt swings in BP. Perioperative use of beta-blockers is important and the use of atenolol, metoprolol, and labetalol has been described.[134] A new selective beta$_1$-adrenergic blocker, landiolol, has been used to prevent further dilatation of the aortic root in a woman with MFS undergoing cesarean delivery under spinal anesthesia.[135] Landiolol can be continuously infused at a rate of 0.04 mg/kg/min in order to maintain heart rate at 80–90 bpm (beats per minute). Calcium channel blockers also are useful for controlling BP in these patients.[136] The use of beta-agonists, vagolytics, and ergot derivatives should be avoided because they may cause a rapid rise in CO and increase the risk of dissection. Atropine should be used carefully to treat bradycardia-induced hypotension. Vasodilators, such as nitroglycerin and nitroprusside, when used as a sole agent, cause an increase in left ventricular ejection velocity by reducing SVR and afterload, which in turn leads to stress on the aortic root. If hypertension occurs, therefore, it is best managed by the concurrent use of labetalol and nitrate infusions.[116]

Some reports describe the anesthetic management of C/S in women with MFS complicated by aortic dissection.[133,134,137,138,139] Concomitant surgical treatment of the dissection usually follows immediately after delivery of the neonate. General anesthesia is used in such cases, with central venous lines, arterial cannulae, and TEE in place to provide adequate monitoring of cardiovascular function. Other reports describe the use of epidural, spinal, and general anesthetics in women with MFS undergoing C/S alone. These women either have aortic root dilatation, or have had prior aortic valve replacement, repair of a prior dissection, or an existing Type B dissection.[134,135,136,137,138,139,140] The principles for successful anesthetic management involve control of BP, avoidance of shear stress across the aortic root, and vigilance for at least 72 hours postpartum.

Other anesthetic considerations in women with MFS include potential airway management problems secondary to high arched palate and the potential for cervical spine instability. Despite the high incidence of bony and ligamentous abnormalities in patients with MFS, a routine cervical radiograph prior to general anesthesia is not recommended.[140] Another concern is the potential for dural ectasia in patients with MFS. Dural ectasia is the expansion of the dural sac surrounding the spinal cord causing low back pain, headache, proximal leg pain, weakness and numbness above and below the knee, and genital/rectal pain. These symptoms are moderate to severe, typically occur daily or several times a week, and are commonly exacerbated by the upright posture but not always relieved by recumbency.[141] Two cases of failed subarachnoid block for cesarean delivery have been described in women with MFS who had dural ectasia confirmed by CT.[142]

Moyamoya disease

Moyamoya disease (MMD) is a condition of unknown etiology characterized by progressive narrowing and occlusion of basal cranial vessels with secondary neoangiogenesis.[143] It commonly affects the terminal portions of the intracranial carotid arteries. Moyamoya disease is uncommon outside of East Asia; however, in Japan the incidence of MMD is 5 per 100 000 population with a female to male ratio of 1.8:1.

Clinical characteristics, diagnosis, and management

Moyamoya disease (see Table 3.5) usually presents in the first decade of life with transient ischemic attacks and then peaks again in

Table 3.5 Moyamoya disease

Etiology unknown
Most common in Japanese
Female:male ratio = 1.8:1
Two onset peaks
- first decade (juvenile) – often presents with TIA
- third and fourth decade (adult) – often presents with cerebral hemorrhage

Pathology
- occlusion and narrowing of internal carotid arteries and distal branches
- cerebral artery aneurysms
- secondary enlargement of perforator arteries around basal ganglia (*puff of smoke* appearance on angiography)

Clinical risks
- cerebral infarction
- cerebral hemorrhage
- seizures

Treatment
- anticoagulants
- platelet inhibitors
- cerebral vasodilators
- anticonvulsants
- surgical revascularization techniques

Goals of anesthetic management
- pain-free vaginal or cesarean delivery
- maintain normocarbia
- avoid hypotension and severe hypertension
- epidural anesthesia has been successfully used
- best to avoid spinal anesthesia in order to avoid large fluctuations in BP

TIA = transient ischemic attack

the third and fourth decades presenting with symptoms of cerebral hemorrhage. It may be associated with intracranial aneurysms in about 15% of cases.[144] Symptoms may be precipitated by hypocarbia due to hyperventilation, or by hyperthermia causing an increase in the cerebral metabolic rate for oxygen ($CMRO_2$). As with other vascular anomalies, the increase in CO that occurs during pregnancy and parturition may precipitate intracranial hemorrhage.

Confirmatory diagnosis is based on the angiographic findings, which characteristically show narrowing of the carotid arteries and/or their distal branches, particularly at the origin of the anterior and middle cerebral arteries. Compensatory enlargement of the perforator arteries around the basal ganglia accompanies the changes in the carotid vessels. In Japanese, "moyamoya" means "something hazy" (like a puff of smoke), and this is the characteristic appearance of the vasculature around the basal ganglia seen on angiography. Periventricular pseudoaneurysms and saccular aneurysms of the circle of Willis can also be seen angiographically in some patients.

Typically these patients receive anticoagulants, aspirin for platelet inactivation, and verapamil for cerebral vasodilatation to help prevent cerebral ischemia. Patients with seizure disorders are maintained on anticonvulsant therapy.[143]

Revascularization surgery is an established treatment of ischemic attacks and includes superficial temporal artery to middle cerebral artery (extracranial/intracranial) bypass and encephaloduroarteriosynangiosis. However, it is uncertain whether these procedures reduce further hemorrhagic events.[143]

Anesthetic management in women with Moyamoya disease

The goal of anesthetic management is to provide a pain-free vaginal delivery or C/S while maintaining cerebral blood flow (see Table 3.5). Hypotension and hyperventilation are avoided as both can decrease cerebral perfusion. Hypertension associated with endotracheal intubation should be anticipated and managed with i.v. lidocaine and antihypertensive drugs, such as labetalol. This will minimize the risk of cerebral hemorrhage, particularly in those who have intracranial aneurysms. Ideally, operative vaginal or abdominal delivery should be performed in order to prevent the hemodynamic consequences of maternal effort.

Regional anesthesia is preferred for labor and C/S as it allows easier neurological assessment of the patient. Epidural and CSE anesthesia have been described in women with MMD.[145,146] Spinal anesthesia is best avoided in order to avoid large fluctuations in BP.[143] One case report described the use of transcranial Doppler to measure cerebral blood flow during C/S under slowly induced epidural anesthesia.[147] However, the value of transcranial Doppler in this setting is uncertain. An arterial catheter is recommended for continuous BP monitoring during labor and delivery.[148]

Kawasaki disease (mucocutaneous lymph node syndrome)

Kawasaki disease (KD) is an acute febrile illness of children under the age of four years. Most investigators agree that an infectious trigger leads to massive activation of the immune system, resulting in a prolonged self-directed immune response at the coronary arteries.[149] The most important clinical features of this disease are coronary arteritis with aneurysms and thrombotic occlusions. These may lead to ischemic heart disease and sudden death. There are reports of adult survivors of KD some of whom become pregnant. A large survey in Japan identified 46 deliveries in 30 patients with KD.[150] One report described a woman with KD who had a successful pregnancy and normal vaginal delivery nine years after a coronary artery bypass graft for a giant coronary artery aneurysm.[151] The large Japanese survey reported mostly vaginal deliveries and the use of epidural analgesia for assisted vaginal births.[150] Mode of delivery was determined primarily on obstetric considerations. Importantly, many women with KD will present in labor on anticoagulants[152] and aspirin therapy. This will need to be taken into consideration when planning neuraxial techniques.

The principles for anesthetic management of women with KD will depend on physical status, the nature and location of the coronary lesion, previous surgery, and current medications.[153,154] (See Chapter 1 for details of the management of coronary artery disease in pregnancy.) These patients are at risk for developing myocardial infarction, ventricular failure, and ventricular dysrhythmias, so a defibrillator should be readily available. The practical management of a parturient with heart disease has been reviewed recently by Dob and Yentis.[155] Low-dose epidural infusions for labor analgesia will be suitable for most women with a history of KD assuming that they are not anticoagulated. This will reduce the stress on the mother and her heart.

Klippel-Trenaunay-Weber syndrome

Klippel-Trenaunay-Weber syndrome (KTWS) is a rare congenital soft-tissue anomaly characterized by multiple hemangiomas, varicose veins, AV fistulas, and unilateral limb hypertrophy.[156] Klipped-Trenaunay-Weber syndrome is thought to occur sporadically, but there is evidence of an autosomal dominant inheritance with familial occurrence.[157,158] Vascular morphogenesis is a vital process for embryonic development, normal physiologic processes (e.g. wound healing), and pathologic processes (e.g. atherosclerosis and cancer). Genetic studies of vascular anomalies have identified critical genes involved in vascular morphogenesis.[159] A susceptible gene, VG5Q, has been cloned for KTWS, which encodes a potent angiogenic factor. Increased angiogenesis is one possible molecular mechanism for the pathogenesis of KTWS. There are many other vascular anomaly genes.[159]

The vascular abnormalities seen in this condition include extensive cutaneous vascular malformations, venous varicosities, and focal abnormalities of the deep venous system. In addition, there is underlying soft-tissue and bony hypertrophy that can give rise to arm and leg asymmetry and facial asymmetry. The latter may give rise to temporomandibular joint dysfunction.[160] Other orthopedic manifestations of KTWS include limb-length discrepancies, digital anomalies, ulcerations, spine and hip abnormalities, and Charcot osteoarthropathy.[161]

Klippel-Trenaunay-Weber syndrome can be diagnosed in utero using routine prenatal ultrasound.[162,163] Women with KTWS can

become pregnant and there are a number of case reports describing KTWS and pregnancy.[164,165,166,167] Klippel-Trenaunay-Weber syndrome is associated with bleeding from angiomata in the genitalia and coagulation disorders. Uterine angiomatosis[168] may lead to placental insufficiency and fetal growth restriction.[169] Kasabach-Merritt coagulopathy, defined by thrombocytopenia and a consumptive coagulopathy, can complicate KTWS during pregnancy especially if there are extensive hemangiomas.[170] This has obvious implications for the obstetric anesthesiologist.

Major conduction anesthesia has been described in women with KTWS during pregnancy, but it is prudent to obtain MRI or CT studies to rule out AV malformations of the lumbosacral spine.[171,172] Epidural needles should not be placed through a cutaneous port-wine lesion.[171,173]

Splenic artery aneurysm

This uncommon aneurysm has the potential to grow and rupture during pregnancy with life-threatening, often fatal, results for the mother and fetus.[174] Splenic artery aneurysm (SAA) occurs predominantly in women, and a majority of the aneurysms are asymptomatic until rupture. Over half of those that rupture do so during pregnancy or in women who have had children.[175] A rupture of the splenic artery can mimic uterine rupture, severe placental abruption, ectopic pregnancy, and most acute abdominal emergencies. It may also mimic cardiorespiratory arrest from pulmonary embolism.[176] A case of SAA at a hospital in San Diego occurred on the postpartum unit in an obese woman who complained of chest pain and shortness of breath. During evaluation of her symptoms and treatment of hypoxemia she had a cardiac arrest with electromechanical dissociation (EMD) and efforts at resuscitation failed. Postmortem examination revealed a large hemoperitoneum and a ruptured splenic artery aneurysm. Patient survival has been described when timely laparotomy is performed and treatment started with rapid infusion of i.v. fluids and blood products, ligation of the proximal splenic artery, and splenectomy.[177] Awareness of the possibility of splenic artery aneurysm rupture is key to timely and successful resuscitation.

Summary

This chapter has dealt with uncommon vascular disorders that have the potential to cause significant morbidity and mortality to mother and fetus. A more common cause of maternal mortality from a vascular disorder is venous thromboembolism, which has an incidence of 1 per 1000 deliveries[178] of which 1–2% are fatal.[179] Acquired or inherited thrombophilias augment the risk. Arterial thrombosis is a feature of a number of the uncommon conditions reviewed, and the incidence of ischemic stroke during pregnancy is estimated at 0.18 per 1000 deliveries. Risk factors for arterial thrombosis include advanced maternal age, atherosclerosis, obesity, hypertension, and smoking. Other important risk factors include prosthetic heart valves and drugs that cause vasospasm.[180] Obstetric anesthesiologists need to be aware that women with predisposition to vascular disease or those with preexisting vascular lesions may become symptomatic during pregnancy with clinically significant results.

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4 RESPIRATORY DISORDERS IN PREGNANCY

John Philip and Shiv K. Sharma

Adult respiratory distress syndrome

Epidemiology

Adult respiratory distress syndrome (ARDS) is a severe form of acute respiratory failure that can develop following a systemic or pulmonary insult. Adult respiratory distress syndrome is not unique to adults, and in children is known as "*acute* respiratory distress syndrome". The incidence of ARDS in pregnancy is variably reported as 1 in 3000 to 1 in 6000 deliveries[1] with mortality as high as 44%.[1,2,3,4]

Etiology

Several disorders can cause ARDS in pregnancy (see Table 4.1). Sepsis, secondary to pyelonephritis, chorioamnionitis, or endometritis, is a common cause of ARDS in pregnancy.[1,2,5] Other causes include obstetric hemorrhage, severe preeclampsia, and aspiration.[1,2,5] There may be a combination of sepsis, shock, and fluid overload, the latter of which can be exacerbated by tocolytic therapy.

Pathophysiology

Following the initial insult, a number of inflammatory mediators such as tumor necrosis factor and interleukins 1, 6, and 8 are released. Neutrophils are activated to release other mediators such as reactive oxygen (O_2) species and proteases. These mediators produce widespread microvascular and alveolar epithelial damage. Microvascular damage leads to increased capillary permeability and subsequent interstitial and alveolar edema. Alveolar damage results in loss of surfactant and subsequent alveolar collapse. Alveolar edema and collapse contribute to ventilation–perfusion (V/Q) mismatching and intrapulmonary shunting with subsequent hypoxemia.

Pulmonary hypertension frequently develops leading to right ventricular (RV) dysfunction which reduces left ventricular (LV) preload and cardiac output (CO). Depressed CO further compromises O_2 delivery. Multisystem organ failure eventually ensues and is a common cause of death (see Figure 4.1). Recent extensive reviews of pathophysiology are provided elsewhere.[6,7]

Clinical course

The pulmonary manifestations of ARDS develop within 24–48 hours of the initial insult. Initially, tachypnea may be the only finding, followed by dyspnea and hypoxemia. Further progression results in audible changes on lung auscultation, and radiological evidence of diffuse pulmonary infiltrates.

Worsening hypoxemia impairs O_2 delivery to tissues causing multisystem organ dysfunction, typically acute renal failure, disseminated intravascular coagulopathy, and hepatic failure. Multisystem organ failure is the main cause of death.

Diagnosis

The clinical spectrum of ARDS is wide. In 1994, the American–European consensus conference on ARDS[8] issued the following definition that has been widely adopted by clinicians and researchers. ARDS is characterized by: (1) bilateral radiographic pulmonary infiltrates; (2) PaO_2 to FiO_2 ratio of 200 or less regardless of the level of positive end-expiratory pressure (PEEP); (3) no clinical evidence of heart failure (if measured, a pulmonary capillary wedge pressure (PCWP) of 18 mmHg or less).

Medical management

The management of ARDS in pregnancy does not differ significantly from that in nonpregnant patients. The main objectives in managing ARDS are to treat the underlying cause, optimize tissue O_2 delivery, and manage the acute lung injury while limiting further lung injury.

General principles of management include provision of respiratory support to ensure adequate oxygenation; support of CO with fluids and inotropes to promote O_2 delivery; correction of anemia to facilitate O_2 delivery; and administration of sedatives, analgesics, and antipyretics to reduce O_2 consumption. Sepsis is commonplace in ARDS and must be aggressively treated with antimicrobial therapy.

Respiratory support

Patients with ARDS require endotracheal intubation and positive pressure ventilation in order to maintain adequate gas exchange and facilitate O_2 delivery. The decision to provide ventilatory support should be made in a timely manner so as to optimize maternal condition and fetal O_2 delivery.

Optimal ventilator settings will provide adequate oxygenation without causing O_2 toxicity, alveolar overdistention, barotrauma, or hemodynamic compromise.[9,10] The lowest inspired O_2 concentration to maintain a PaO_2 greater than 60 mmHg or a SaO_2 greater than 90% will reduce the risk of O_2 toxicity. The use of low tidal volumes in patients with ARDS is associated with lower mortality rates. In one report of more than 800 patients with ARDS, mortality was significantly reduced with low tidal volumes compared with traditional methods of ventilation.[11] However, increased intrathoracic pressures and hypercapnia can result from this strategy. Positive end-expiratory pressure

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Table 4.1 Etiology of adult respiratory distress syndrome in pregnancy

Sepsis
chorioamnionitis
pyelonephritis
endometritis
septic abortion
Infectious pneumonia
Obstetric hemorrhage
shock
massive blood transfusion
Severe preeclampsia
Aspiration
Embolism
thrombotic
amniotic fluid
venous air
trophoblastic
Connective tissue disease
Substance abuse
Inhalation injury
Pheochromocytoma
Drug overdose

Modified from references 1, 2, 5, 36, and 37

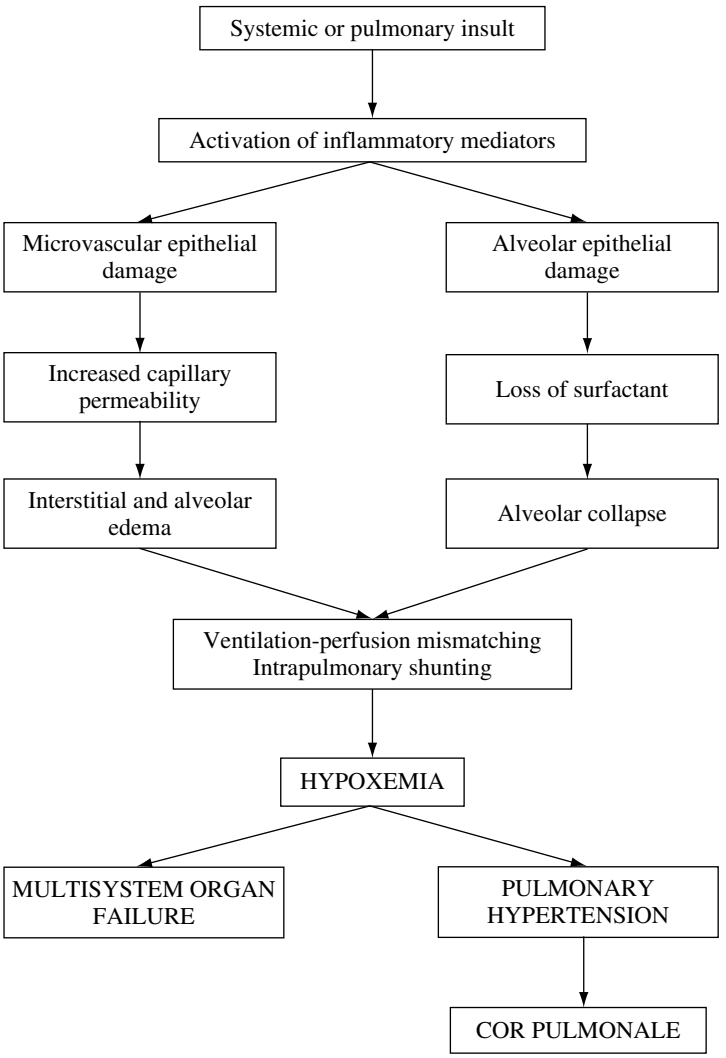


Figure 4.1 Pathophysiology of ARDS.

is used to prevent alveolar collapse, recruit collapsed alveoli, and improve oxygenation. However, excessive levels of PEEP can decrease CO, reduce O_2 delivery, and increase the risk of barotrauma.

Nitric oxide (NO) relaxes smooth muscle, and when inhaled facilitates pulmonary vasodilation in ventilated areas of the lung. In turn, this minimizes intrapulmonary shunting and improves O_2 delivery. Inhaled NO therapy for ARDS improves oxygenation but does not change mortality.[12,13] There are reports of the use of inhaled NO in pregnancy, including one report of a pregnant woman with fulminant respiratory failure.[14] The potential benefit of inhaled NO in carefully selected patients with intractable hypoxemia cannot be ruled out.[15]

Another pharmacological approach to the treatment of ARDS has been the use of exogenous surfactant. Although preliminary studies seemed promising, no benefit in reducing mortality from ARDS has been demonstrated with the use of recombinant or synthetic surfactant.[16,17]

Fluid management

Fluid balance can be difficult to achieve in ARDS. Widespread capillary leak with extravasation of fluids, plus intravascular hypovolemia, can depress CO and compromise tissue O_2 delivery. However, intravenous (i.v.) fluid administration to correct hypovolemia may precipitate pulmonary edema and worsen tissue O_2 delivery. Furthermore, the lower colloid oncotic pressure of pregnancy may predispose a pregnant woman with ARDS to a greater risk of pulmonary edema. The PCWP should be kept at the lowest level compatible with adequate CO. Fluid balance is maintained using crystalloid solutions to increase intravascular volume or diuretics to reduce intravascular volume when needed, using data from pulmonary artery catheterization to guide therapy.

Other therapies

Since much of the lung damage from ARDS is caused by inflammatory mediators, it has been hypothesized that pharmacological agents capable of suppressing inflammation and promoting lung repair could positively impact clinical outcomes. However, various novel anti-inflammatory and antioxidant therapies have not yielded promising results.[18,19,20,21,22,23] The value of corticosteroid therapy in ARDS is uncertain, although there is recent evidence of a possible benefit in unresolving ARDS.[24]

Prospective randomized trials have failed to show an advantage of extracorporeal membrane oxygenation (ECMO) over conventional treatment in patients with ARDS. However, case reports have described recovery from ARDS in pregnancy following the use of ECMO.[25]

Selective decontamination of the digestive tract, to limit translocation of gut pathogens, can reduce mortality in critically ill patients.[26]

Obstetric management

The risks and benefits of early, elective delivery must be assessed, but no study has demonstrated an improvement in maternal outcome with delivery of the fetus.[5,27,28] However, when the maternal condition is such that placental O_2 transfer is compromised, immediate delivery may be required to minimize perinatal morbidity and mortality. Vaginal delivery is possible in ventilated patients with ARDS[3,29,30,31] and cesarean section (C/S) is typically reserved for obstetric indications.

Anesthetic management

Increased O_2 consumption during active labor is well known. Labor analgesia for mechanically ventilated patients can be provided with i.v. opioids, which in turn can decrease O_2 consumption. However, epidural analgesia has been shown to have a beneficial effect on O_2 consumption in a parturient with ARDS.[32] If a regional anesthetic is considered, attention must be given to intravascular volume, coagulation status, and the presence of infection. Technical factors often will limit the ability to induce regional anesthesia in these women. In mechanically ventilated patients, general anesthesia (GA) is often the most convenient choice of anesthetic for C/S.

Asthma in pregnancy

Introduction

Asthma has been reported to affect 3.7% to 8.4% of pregnant women.[33] The natural course of asthma in pregnancy appears variable, with conflicting reports in the literature.[34,35,36] However, a significant proportion of patients experience a worsening of their symptoms, whereas others may remain unchanged or improve during pregnancy. Baseline asthma severity correlates well with asthma exacerbation during pregnancy. With mild disease, 13% suffer exacerbations, whereas with severe asthma, exacerbations may occur in up to 50% of affected women.[37] Further, the risk of exacerbation following C/S is much higher than with vaginal delivery.[38] Approximately two-thirds of women show the same pattern in their asthma from one pregnancy to the next.[39] Status asthmaticus is a relatively uncommon occurrence in pregnancy and is seen in approximately 0.2% pregnancies.[38]

Maternal and fetal effects of asthma

Mild forms of asthma have minor effects on pregnancy and neonatal outcome.[40] There is a slight increase in the incidence of preeclampsia, preterm labor, low-birthweight infants, and perinatal mortality in pregnant asthmatics.[36,41,42,43] The rate of intrauterine growth restriction increases as the severity of asthma worsens, possibly due to maternal hypoxemia, increased systemic and pulmonary vascular resistance, and decreased CO.[41] Maternal and perinatal mortality increases when asthma control is poor,[40] or in severe asthmatics when mechanical ventilation is required. Cesarean section is more likely in asthmatics.[34,35,44] Babies of mothers with severe asthma are more prone to hypoglycemia as a result of maternal treatment with steroids.[34]

Management of asthma

The characteristics of asthma include reversible airway obstruction from bronchial smooth muscle contraction, mucus hypersecretion, and mucosal edema. This chronic inflammatory airway disorder is exacerbated by release of histamine, prostaglandin D2, and leukotrienes from mast cells after exposure to stimulants such as cigarette smoke, viral infections, aspirin, cold air, or exercise. There is evidence that heredity plays a major role in the development of asthma.[45,46]

Clinical course

The clinical course of asthma depends on the degree of bronchospasm and subsequent alterations in oxygenation due to V/Q mismatching. Affected women typically present with chest tightness, wheezing, or breathlessness. Mild asthmatics usually develop respiratory alkalosis due to hyperventilation resulting in decreased pCO_2, with normal arterial pO_2. Ventilation perfusion mismatch worsens as asthma becomes more severe leading to arterial hypoxemia, hypercapnia, acidemia, and, if untreated, respiratory failure. Even mild asthma is a threat to the pregnant woman and her fetus, as pregnant women have reduced respiratory reserves and are more susceptible to hypoxemia.

Evaluation

Clinical examination, arterial blood gas analysis and pulmonary function tests are required to determine the severity of asthma. Clinical signs of severe disease include labored breathing, tachycardia, pulsus paradoxus, prolonged expiration, central cyanosis, and altered consciousness. Arterial blood-gas analysis provides objective assessment of maternal oxygenation, ventilation, and acid-base status. Measurement of the forced expiratory volume in one second (FEV_1), which correlates with the peak expiratory flow rate (PEFR), is now used routinely in the assessment of severity and management of asthma. $FEV_1 < 1$ L indicates severe disease with hypoxia and poor response to therapy.[47]

Management of chronic asthma

Experts agree that undertreatment is the single most important error in the management of asthma during pregnancy.[36,39] Pregnant women and their physicians should be reassured that most of the regularly used drugs (including albuterol, terbutaline, epinephrine, methylxanthines, cromolyn, oral steroids, and inhaled beclomethasone) have been used widely for many years without any evidence of teratogenicity in humans.[46,47,48] One study

Table 4.2 Usual doses of medications for chronic asthma during pregnancy and lactation

Medication	Adult dose
Inhaled corticosteroids	
Beclomethasone CFC 42 or 84 μg/puff	168–840 μg/day
Beclomethasone HFA 40 or 80 μg/puff	80–480 μg/day
Budesonide DPI 200 μg/inhalation	200–600 μg/day
Systemic corticosteroids	*Applies to all three corticosteroids*
Methylprednisolone	7.5–60 mg daily
Prednisolone	Short-course "burst" to achieve control:
Prednisone	40–60 mg per day as single dose or two divided doses for 3–10 days
Long-acting inhaled beta 2-agonists (preferably with inhaled corticosteroids)	
Salmeterol MDI 21 μg/puff	2 puffs q 12 hours
Formoterol DPI 12 μg/single-use capsule	1 capsule q 12 hours
Cromolyn	
Cromolyn MDI 1 mg/puff	2–4 puffs tid-qid
Leukotriene receptor Antagonists	
Montelukast 10 mg tablet	10 mg qhs
Zafirlukat 10 or 20 mg tablet	40 mg daily (20 mg tablet bid)
Methylxanthines (serum concentration of 5–12 μg/ml at steady state)	
Theophylline	Starting dose 10 mg/kg/day up to 300 mg max: usual max 800 mg/day

MDI = metered-dose inhaler; DPI = dry powder inhaler; CFC = chlorofluorocarbon; HFA = hydrofluoroalkane
(NB 100 μg beclomethasone CFC (budesonide) is equivalent to 50 μg beclomethasone CFC-free (fluticasone) because the CFC-free product has superior lung deposition. HFA is a nonozone depleting propellant. CFC is an ozone depleting propellant that is to be phased out of production by international agreement).

Table 4.3 Pharmacologic step therapy of chronic asthma during pregnancy

Category	Step therapy
Mild intermittent	Inhaled beta 2-agonists as needed (for all categories).
Mild persistent	Inhaled cromolyn. Continue inhaled nedocromil in patients who have shown a good response prior to pregnancy. Substitute inhaled corticosteroids (see below) if above not adequate.
Moderate persistent	Inhaled corticosteroids. Continue inhaled salmeterol in patients who have shown a very good response prior to pregnancy. Add oral theophylline and/or inhaled salmeterol for patients inadequately controlled by medium-dose inhaled corticosteroids.
Severe persistent	Above plus oral corticosteroids (burst for active symptoms, alternate-day or daily if necessary).

ACAAI/ACOG recommendations (Ref. 59)

found that maternal exposure to orally inhaled budesonide during pregnancy is not associated with an increased risk of congenital malformations or other adverse fetal outcomes.[49] Table 4.2 shows some common drugs and the doses used for chronic asthma.

Corticosteroids are anti-inflammatory agents that have three distinct actions on gene expression and second messenger cascades.[50] The risk associated with use of oral corticosteroids during pregnancy is probably still less than the potential risks to the mother and the fetus from severe asthma. The low plasma levels achieved by inhaled corticosteroid make it unlikely that fetal effects will occur. Beta-2 adrenergic agonists activate adenyl cyclase to increase intracellular 3′-5′-cyclic adenosine monophosphate (cyclic AMP) and cause bronchial smooth muscle relaxation. Women with asthma should measure and record PEFR twice daily. The baseline values range from 380 to 550 L/min in pregnant women. Treatment depends on the severity of disease (see Table 4.3).[49] For mild asthma, inhaled beta-agonists are used every three to four hours as needed, but inhaled corticosteroids are recommended for persistent asthma. The use of inhaled corticosteroids along with a beta-agonist may reduce hospital readmission for a severe exacerbation. Theophylline is a methylxanthine and a bronchodilator with possible anti-inflammatory effects. This agent is useful for oral maintenance therapy if patients do not respond to inhaled corticosteroids and beta-agonists. Reduced plasma protein binding of theophylline in pregnancy increases the availability of free (active) drug. Recommended plasma therapeutic ranges in pregnancy are between 5–12 μg/ml or 8–15 μg/ml.[51] A comparison of oral theophylline with inhaled beclomethasone, for maintenance therapy in pregnant women with asthma, showed no difference in exacerbation rates and no difference in pregnancy outcome.[52] However, women tend to discontinue oral theophylline because of its side effects.

Cromolyn and nedocromil, which inhibit mast cell degranulation, are used to prevent asthma, but are ineffective for treatment of acute asthma. They are administered as aerosols and clinical experience suggests that fetal effects are minimal. Leukotriene modifiers (zileuton, zafirlukast, and montelukast) inhibit leukotriene synthesis. These agents provide slightly improved asthma control when given either orally, or by inhalation, for prevention of asthma.[53] There is minimal information

Table 4.4 Management options of status asthmaticus

Drug	Route	Dose	Comments
Oxygen	face mask	40–60%	Humidification important
Heliox	face mask	70–80% helium, 20–30% oxygen	
Beta-2 adrenergic agonists			
Terbutaline	neb.	10 mg	
Terbutaline	s.c.	0.25 mg	Repeat after 15–30 min, beware of hypotension
Albuterol	neb.	5 mg	
Epinephrine	s.c.	0.3 mg	Repeat after 20 min × 2
Steroids			
Methylprednisolone	i.v.	60–125 mg	Steroids ↑ gestational diabetes + fetal hypoglycemia
Hydrocortisone	i.v.	100–200 mg	Cover stressful events (e.g. delivery)
Prednisone/prednisolone	o	30–60 mg daily	
Methylxanthine			
Theophylline	i.v. (slowly)	5 mg/kg loading dose	↓ if previous doses or on theophylline
	infusion	0.2–0.9 mg/kg/hr	Check plasma theophylline levels
			Therapeutic range?
Anticholinergic			
Ipratropium	neb.	0.5 mg	Works best in combination therapy

neb. = nebulized; s.c. = subcutaneous; i.v. = intravenous, o = oral

currently available on the use of leukotriene modifiers during human pregnancy (see www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg/astpreg_qr.pdf).

Management of acute asthma

The key to the successful treatment of acute asthma during pregnancy is a low threshold for hospital admission. Careful clinical assessment must be made upon admission and reviewed frequently. Treatment goals include minimizing hypoxemia, hypercarbia, or alkalosis, all of which reduce fetal oxygenation. Intravenous fluid administration helps to clear pulmonary secretions through hydration, and supplemental O_2 by mask should be administered after a blood-gas sample is obtained. It is recommended that pO_2 be maintained at > 60 mmHg, and $SaO_2 > 95\%$. Monitoring includes continuous pulse oximetry and electronic fetal heart rate.

First-line therapy for acute asthma includes inhaled or subcutaneous (S/C) beta-adrenergic agonists (see Table 4.4), and corticosteroids should be given early when asthma is severe.[54] Intravenous methylprednisolone 40 to 60 mg, every six hours, or equipotent doses of hydrocortisone by infusion, are given in conjunction with beta-agonists.

If initial therapy with beta-agonists fails to improve FEV_1 or PEFR to >70% baseline values, or if respiratory distress persists, admission to an intensive care unit is recommended. An elevated arterial pCO_2 (>38 mmHg) is an ominous sign in pregnancy but would be considered normal in a nonpregnant woman.

Intensive therapy includes inhaled beta-agonists, i. v. corticosteroids, and close observation for worsening respiratory distress or fatigue in breathing.[55] Severe asthma of any type not responding to 30–60 minutes of intensive therapy is termed status asthmaticus. Management of nonpregnant patients with status asthmaticus in an intensive care setting results in a good outcome in most cases.[56] Fatigue, CO_2 retention, and persistent hypoxemia are indications for mechanical ventilation.

Intravenous albuterol, terbutaline, and ritodrine have well-known tocolytic effects and are often used to treat preterm labor. However, there is no evidence that these drugs interfere with the course of labor when used by the inhaled or s. c. routes.

Intubation and ventilation

If endotracheal intubation is required, aortocaval compression must be avoided and induction of anesthesia should include preoxygenation and precautions against aspiration of gastric contents. Thiopental, etomidate, and ketamine have been used as induction agents, but the marked bronchodilator properties of ketamine make it the preferred agent. However, seizure-like extensor spasms have been reported following the administration of ketamine to patients who had received aminophylline, so caution is necessary.[57] Alternatively, propofol, which provides better protection against bronchospasm than thiopental, can be used. The risk of histamine release from succinylcholine is outweighed by the excellent intubating conditions achieved. Intravenous lidocaine 1 mg/kg has been advocated to minimize further bronchospasm.[58] The alternative technique of using an inhalational induction with sevoflurane is unlikely to be smooth or easy; moreover it may increase the risk of pulmonary aspiration, and is not recommended. Once the trachea is intubated, high concentrations of volatile anesthetic agent can be used to break the bronchospasm.

Muscle relaxation should be provided by nondepolarizing agents that do not release histamine (e.g. vecuronium). Peak airway pressures are likely to be high and careful manipulation of ventilator settings is required to minimize the risk of barotrauma (pneumothorax and pneumomediastinum). Normal physiological (pregnant) values for arterial pO_2 and pCO_2 are the desired endpoint. The use of PEEP is controversial in this setting.

Labor and delivery

Asthma medications are continued throughout delivery. Additional corticosteroids are administered if systemic steroid therapy was used within four weeks. Hydrocortisone 100 mg i.v. every eight hours is a commonly used dosing regimen. The PEFR or FEV_1 should be determined upon admission and serial measurements taken if symptoms develop.

Epidural analgesia markedly reduces the work and physiological stress of labor[59] and is strongly recommended for asthmatic parturients. A weak bupivacaine-opioid solution has been used successfully to produce minimal motor block, and avoid respiratory embarrassment.[60] A combined spinal–epidural technique (CSE) may also provide rapid onset of good quality analgesia with minimal motor block.[61] However, aseptic meningitis has been reported following CSE and high-dose steroids may, theoretically, increase the risk of this complication. Paracervical and pudendal blocks may be used for the first and second stages of labor, respectively, when epidural or spinal analgesia is unsuitable. An assisted delivery (forceps or vacuum extraction) minimizes maternal stress and effort.

If regional anesthesia is contraindicated, opioids (preferably i.v. ± patient controlled) may be used but provide less effective analgesia, particularly for the second stage of labor. Fentanyl is the preferred opioid for asthmatic patients since it does not release histamine. Careful assessment must be made of the effects of opioid analgesia on respiratory function.

Cesarean section

When C/S is necessary for women with asthma, regional anesthesia is preferable, since it avoids airway stimulation. However, acute bronchospasm has been precipitated by spinal anesthesia in pregnancy, although the etiology was unclear.[62] It is postulated that high sensory blockade causes a fall in adrenal epinephrine output,[63] but this should not be a reason to avoid regional anesthesia. Although spinal anesthesia provides a rapid block, epidural anesthesia allows slow incremental titration, which may minimize the risk of respiratory embarrassment from a high sensory level. However, the sensory level must be high enough to provide good-quality analgesia (above T6 sensory level), since intraoperative pain and distress can worsen bronchospasm. The addition of an epidural opioid (e.g. fentanyl or sufentanil) improves the quality of the sensory block and is recommended. Epidural epinephrine use is still controversial in obstetric anesthesia and risks a potential additive effect with other $beta_2$-adrenergic agonists, particularly S/C epinephrine. Many anesthesiologists, however, still use epinephrine in the initial test dose.

Table 4.5 Anesthetic and obstetric drugs to avoid

Prostaglandin $F_{2\alpha}$
Ergonovine
Aspirin and other NSAID
Histamine-releasing drugs (e.g. atracurium, tubocurare)

NSAID = nonsteroidal anti-inflammatory drugs

If the woman's condition is too poor to tolerate a regional technique (i.e. restless, dyspnoeic, and unable to lie supine), GA is required. The management of endotracheal intubation is described above. Nitrous oxide may increase the degree of air trapping, reduce the maximum O_2 concentration, and probably adds little value to the anesthetic technique. Maintain anesthesia with a halogenated inhalation agent at a concentration high enough to avoid "light" (i.e. inadequate) anesthesia, since inadequate anesthesia will aggravate bronchospasm. Excessive blood loss due to uterine atony is unlikely to be a significant problem when using halothane 0.75%, enflurane 1.7%, or isoflurane 1.2% in O_2 after a short period of overpressure.[64] Sevoflurane is an effective agent in preventing and managing intraoperative bronchospasm.[65]

Intravenous oxytocin infusion should be used routinely after delivery to provide uterine contraction. Ongoing hemorrhage from uterine hypotonia, despite oxytocin administration, is treated with prostaglandin E_2 or methergine (ergonovine). Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) may cause significant bronchospasm in asthmatic patients (see Table 4.5). Oxygen desaturation following 15-methyl $PGF_{2\alpha}$ has been reported in women without reactive airway disease.[66]

After GA, intensive care admission is advised as it allows for a delayed and controlled extubation with optimization of respiratory and cardiovascular parameters. In view of the potential to aggravate bronchospasm, some practitioners avoid nonsteroidal anti-inflammatory drugs (NSAID), providing postoperative analgesia with continuous regional techniques or parenteral opioids.

Summary

The greatest risk to an asthmatic mother and her baby stems from inadequate treatment of acute asthma. All the drugs commonly used in the treatment of acute asthma are reliable, and safe to use in pregnancy. They should not be withheld from the mother on the basis of potential, unproven and unlikely toxic effects on the fetus. A low threshold for hospitalization is important for the successful treatment of acute asthma in pregnant women. Regional anesthesia and analgesia have important advantages in this patient population, not least of which is avoidance of airway stimulation.

Pulmonary embolism

Introduction

Pulmonary embolism is a significant cause of morbidity and mortality during pregnancy.[67,68] Emboli may consist of

thrombus, air, or amniotic fluid, and rarely of fat, tumor, sickle cell, or infectious material. Amniotic fluid embolism (AFE) is a rare entity with usually catastrophic outcome. In contrast, venous air embolism (VAE) occurs commonly, but is associated with a less severe clinical course.

Thromboembolic disease

Incidence

Pulmonary thromboembolism (PTE) is a complication of venous thrombosis. The risk of venous thromboembolism has been estimated to be fivefold to sixfold higher in women who are pregnant compared to nonpregnant women.[68,69] Deep vein thrombosis (DVT) occurs in 1 in 300 to 1 in 5000 of all pregnancies and there is evidence that the incidence is more common in the antepartum period.[70,71,72] Pulmonary thromboembolism occurs mostly as a result of DVT, and rarely from superficial, pelvic, or ovarian vein thromboses. Pulmonary thromboembolism complicates 1 in 1000 to 1 in 2000 pregnancies and accounts for approximately 12% to 25% of direct maternal mortality.[73,74]

Etiology

The uterus grows as pregnancy progresses and may compress the inferior vena cava, resulting in venous stasis in the pelvic and lower extremities. In pregnancy, blood is hypercoagulable in that several coagulation factors (e.g. fibrinogen V, VII, VIII, X, XII, and von Willebrand factor) increase, while naturally occurring anticoagulants (antithrombin III, proteins C and S) decrease.[75] Increased platelet reactivity, as a result of enhanced thromboxane A2 (TXA2) production, further contributes to the hypercoagulability during the third trimester of normal pregnancy.[76]

Vascular trauma during C/S and vaginal delivery and separation of the placenta may initiate a series of physiologic events leading to an acceleration of coagulation activity and increased risk of thromboembolism. The risks of DVT and PTE are five to fifteen times higher after C/S than after vaginal delivery.

Table 4.6 shows some coexisting factors and conditions, which increase the risk of PTE in pregnancy.

Table 4.6 Coexisting factors and conditions that increase the risk of pulmonary thromboembolism in pregnancy

Smoking
Obesity
Preeclampsia
Multiple gestation
Previous history of thromboembolism
Antiphospholipid antibody syndrome
Proteins S and C deficiencies
Antithrombin III deficiency
Hyperhomocysteinemia
Prothrombin gene mutation
Factor V Leiden mutation

Resistance to activated protein C, which is frequently associated with Factor V Leiden mutation, is by far the most common identified genetic predisposition to the development of thrombosis.[77,78] Other thrombophilic states that interact with the procoagulant state of pregnancy include: antithrombin deficiency, protein S deficiency, and MTHFR C677T homozygotes.[78]

Pathophysiology

Pulmonary thromboembolism leads to obstruction of the pulmonary arterial tree. In turn there is an increase in pulmonary vascular resistance (PVR) and RV afterload, which can cause RV failure. Massive PTE increases RV afterload acutely and enlarges the right ventricle. There may be a shift of the ventricular septum to the left, which can cause LV failure. Consequently, the increase in hydrostatic pressure and disruption of the normal capillary integrity predispose the patient to pulmonary edema.

Pulmonary thromboembolism causes an increase in V/Q mismatching, especially an increase in the alveolar dead space, which leads to arterial hypoxemia. A decrease in CO in patients with RV failure further enhances the effects of V/Q mismatching. Hypoxemia and hypocapnia are characteristic of PTE.

Clinical presentation

Deep vein thrombosis

Pulmonary emboli occur in 50% of patients with documented DVT. Half of the patients with documented DVT are asymptomatic. Most clinically significant emboli arise from thrombi in the deep veins of the thigh. Calf vein thromboses rarely produce large emboli. The most common signs and symptoms of DVT are swelling of calf muscles (with a 2 cm difference in leg circumference at the mid-calf between the affected and unaffected legs), pain, tenderness, positive Homan sign (painful passive dorsiflexion of the foot), a change in limb color, and a palpable cord due to associated thrombophlebitis. Puerperal ovarian vein and pelvic vein thromboses may present in the postpartum period with a fever lasting more than 72 hours which is unresponsive to antibiotic therapy.

Pulmonary thromboembolism

The clinical diagnosis of PTE is difficult because the presenting signs and symptoms may be nonspecific. Most PTE are asymptomatic and not life-threatening. The common presentations of PTE are listed in Table 4.7. The classic triad of dyspnea, pleuritic pain, and hemoptysis is present in only 25% of patients with PTE. Examination of the cardiovascular system reveals tachycardia, and signs of RV failure (e.g. split-second heart sound, jugular venous distension, a parasternal heave, and hepatic enlargement). Low-grade fever, cyanosis, diaphoresis, altered mental status, wheezing, and clinical signs of DVT may also be present. Rarely, patients may present with abdominal pain due to infarcted lung next to the diaphragm, or disseminated intravascular coagulation (DIC).

Table 4.7 Signs and symptoms of pulmonary embolism

No symptoms
Tachycardia, tachydysrhythmias
Chest pain
Tachypnea
Flank pain
Chest x-ray findings:
atelectasis
pleural effusion
elevated hemidiaphragm
peripheral segmental or subsegmental infiltration
Dyspnea
Hypotension
Hemoptysis
Jugular vein distension
Low-grade fever
Accentuated P2
Syncope
Right-side S3
Unexplained shock
Cyanosis

Diagnosis

Deep vein thrombosis

Compression ultrasonography is noninvasive and is the primary test used currently to detect DVT. It has a sensitivity of 97% and a specificity of 94% for the diagnosis of symptomatic, proximal DVT and a negative predictive value of 98%.[79,80,81]

Impedance plethysmography measures volume changes within the leg. It is only 50% sensitive for detection of a clot in the small calf veins.[82] Furthermore, thrombotic and nonthrombotic occlusions cannot be differentiated by plethysmography.

Invasive venography is the most accurate test for diagnosis of DVT, and has a negative predictive value of 98%.[83] However, it is not useful for the evaluation of the pelvic vasculature, is time consuming and cumbersome, and has significant complications compared to popular noninvasive methods.

Isotope scanning is an effective method of diagnosing DVT. It involves the use of ^{125}I-labeled fibrinogen and its detection as it incorporates into the developing thrombus. Since this method involves systemic injection of radioactive isotope of iodine, which may cross the placenta and affect the fetus, its use is contraindicated during pregnancy. Computerized axial tomography and magnetic resonance imaging (MRI) have been shown to be sensitive in the diagnosis of DVT and to follow the clinical resolution of puerperal ovarian vein and septic pelvic vein thromboses.[82,83]

Pulmonary thromboembolism

A decrease in SaO_2 and end-tidal CO_2 ($EtCO_2$) reflect the abnormal V/Q relationship and increased physiological dead space that can result from PTE. Table 4.7 shows signs and symptoms of pulmonary embolism.

An ECG may show signs of RV strain, right axis shift, P pulmonale, supraventricular dysrhythmias, and S1, Q3, T3 pattern. However, the most common abnormal ECG findings seen with PTE are ST-segment changes.

The chest radiograph (CXR) is neither specific nor sensitive in the diagnosis of PTE because similar findings are observed with other conditions. Furthermore, in approximately 25–40% of patients with pulmonary embolism the CXR may be normal.[84] However, a CXR helps to diagnose other conditions that can mimic PTE, such as pneumonia and pneumothorax. A negative D-dimer assay can be a reassuring diagnostic test in cases of PTE that are of low clinical suspicion.[84]

Invasive hemodynamic monitoring with a central venous catheter or pulmonary artery catheter may reveal increased central venous pressure (CVP), raised mean pulmonary arterial pressure (PAP), and normal or low pulmonary artery occlusion pressure (PAOP). Monitoring PAOP and CO helps to determine the administration of fluids and inotropic drugs.

A definitive diagnosis can be made with a V/Q scan if there is a high clinical suspicion of PTE and a scan shows high probability for PTE (for example normal ventilation with segmental perfusion defect).[85] The probability of PTE is only 10–40% if the perfusion defect on the lung scan is subsegmental with normal perfusion. Normal perfusion on the lung scan excludes the diagnosis of PTE. However, multiple perfusion defects and V/Q mismatch on the lung scan suggest a high probability of a pulmonary embolus. If the lung scan reveals low probability of pulmonary embolus but the clinical suspicion is high, pulmonary angiography should be considered.

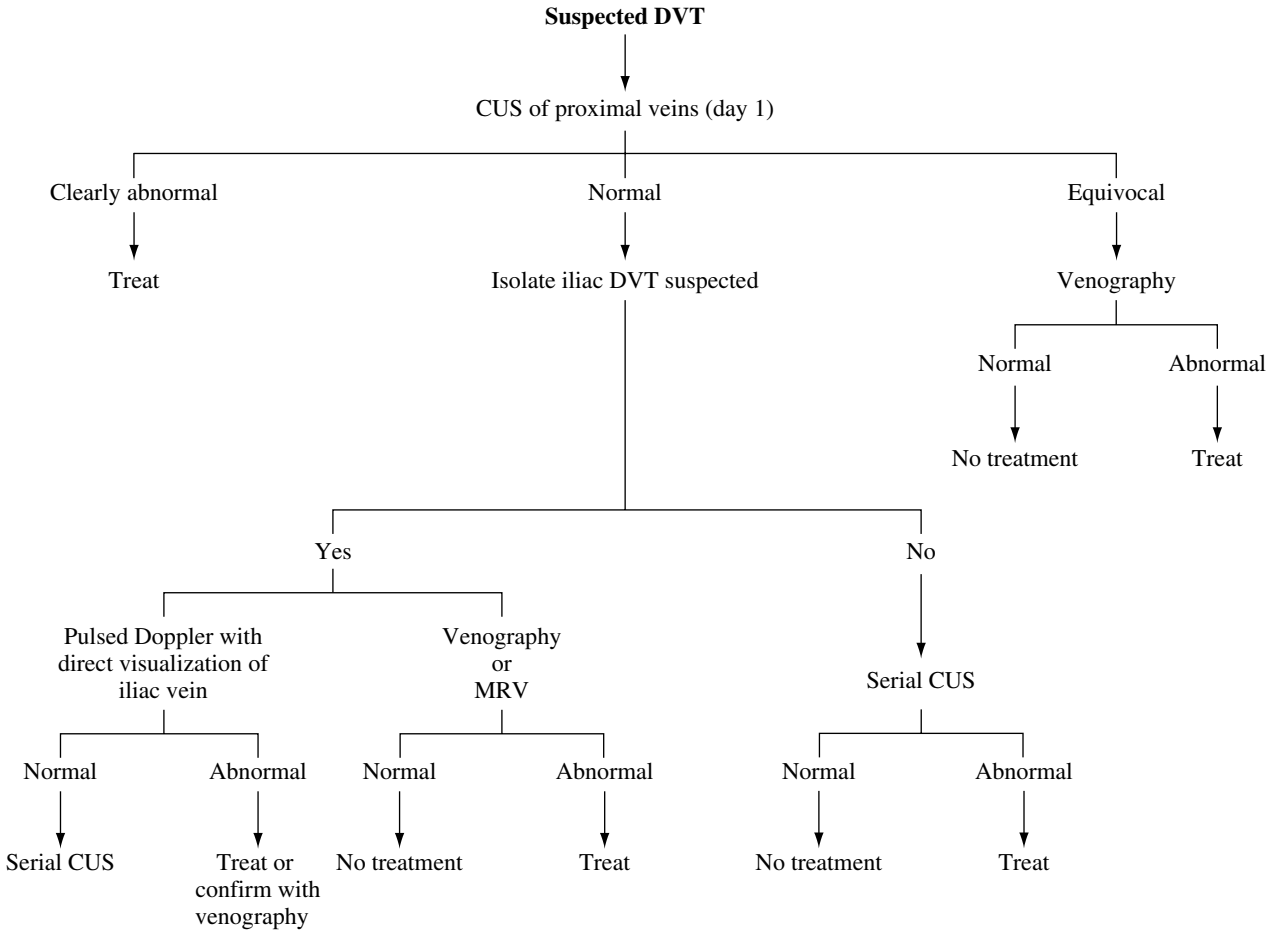
Spiral computed tomography (CT) allows rapid imaging from the main pulmonary arteries to at least the segmental and possibly the subsegmental branches. Fetal radiation exposure with standard spiral CT is less than with V/Q lung scanning.[86]

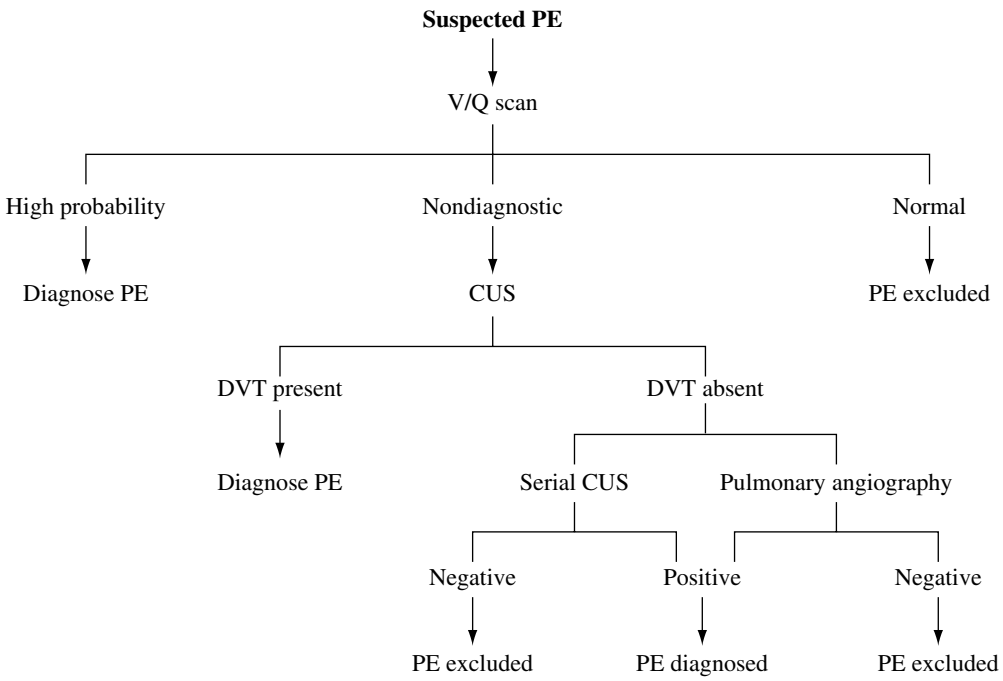
Echocardiography can be useful in the detection of a pulmonary embolus after C/S.[87] Magnetic resonance angiography with i.v. contrast allows high-resolution magnetic resonance angiography during a single suspended breath.[88] Standard pulmonary angiography is currently the most definitive test for PTE, but it is invasive and requires catheterization of the right side of the heart.

Management

Deep vein thrombosis

The clinician should have a high index of suspicion for DVT, but before therapy is started a definitive diagnosis must be established. An algorithm for diagnosis and management of DVT and pulmonary embolism has been proposed (see Figures 4.2 and 4.3)[89] Heparin therapy should be started immediately after the diagnosis of DVT to prevent the occurrence of PTE. The loading dose of unfractionated heparin (UFH) is 100 units/kilogram (U/kg) followed by an initial infusion rate of 1000 U/h. The adequacy of anticoagulation is monitored with serial activated partial thromboplastin times (aPTT), which should be maintained between 1.5–2.5 times normal for 7–10 days.[89] After therapeutic PTT values have been maintained for two days, S/C administration can be substituted for i.v. administration. Subcutaneous





Figures 4.2 and 4.3 An algorithmic approach to diagnosis and management of DVT and pulmonary embolism (from Bates, S. M. & Ginsberg, J. S. How we manage venous thromboembolism during pregnancy. *Blood* 2002; 100: 3470–8). CUS: compression ultrasonography.

Table 4.8 Heparin dosing regimens

Dose	Regimen
Mini-dose UFH	UFH 5000 U subcutaneously every 12 h
Adjusted-dose UFH	UFH subcutaneously every 12 h in doses adjusted to target a midinterval PTT into the therapeutic range
Prophylactic-dose LMWH	Enoxaparin 40 mg once daily or 30 mg twice daily
	Tinzaparin 4500 U once daily
	Dalteparin 5000 U once daily
Weight-adjusted dose LMWH	Enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily
	Dalteparin 100 U/kg every 12 h or 200 U/kg every 24 h
	Tinzararin 175 U/kg once daily

U = units; UFH = unfractionated heparin; LMWH = low molecular weight heparin; PTT = activated partial thromboplastin time

regimens typically use 5000 U of UFH S/C every 12 hours. This dose only minimally prolongs the PTT and theoretically there should be no increased risk of hemorrhagic complications. Heparin therapy may be discontinued when the patient begins active labor or 4–6 h prior to C/S. Baseline anticoagulant activity should be assessed by measuring the PTT immediately after discontinuing the heparin therapy. For surgical hemostasis, the use of protamine in incremental doses up to a calculated dose of 1 mg protamine per 100 U heparin should be considered. Heparin therapy can be reinstituted in the postpartum period if the patient is stable. Warfarin can be administered concurrently, monitoring anticoagulation by the prothrombin time (PT). Anticoagulation is maintained for three months postpartum.

Low-molecular weight heparin (LMWH) does not cross the placenta and has been used effectively in pregnant patients for the prevention and treatment of DVT.[90,91] When compared to UFH, LMWH use during pregnancy has a lower risk of bleeding complications, heparin-induced thrombocytopenia, and osteoporosis. Prophylaxis for PTE includes S/C dalteparin 5000 U every 24 hours or enoxaparin 40 mg every 24 hours (see Table 4.8).[92] The dose of LMWH is adjusted to achieve a peak anti-Xa plasma concentration of 0.4 U/ml to 0.7 U/ml. Optimally, LMWH prophylaxis for patients at risk for thromboembolic disease should continue throughout delivery and into the postpartum period. As with UFH, the pharmacokinetics of LMWH are altered during pregnancy.[93]

Pulmonary thromboembolism

The successful management of a patient with PTE requires prompt diagnosis and rapid institution of appropriate therapy (see Table 4.9). The first hour after a PTE is the most critical, and approximately 10% of all affected patients die during that period.

Initial supportive management of PTE consists of maintaining oxygenation, ventilation, and hemodynamic status. Hypoxemia should be treated with supplemental O_2 but this may not be adequate because of severe V/Q mismatching and decreased mixed-venous O_2 tension. Mechanical ventilation will be necessary in patients with hemodynamic instability and severe hypoxemia. Improved oxygenation reduces RV afterload and improves hemodynamic status. Volume resuscitation with colloids or crystalloids improves CO and arterial blood pressure. If inotropic support for the RV is required dobutamine is preferable to dopamine because of its vasodilatory effects.

Table 4.9 Management of pulmonary thromboembolism

- Cardiopulmonary support
- Anticoagulation therapy
- Venous interruption
- Fibrinolytic therapy
- Surgical embolectomy

Heparin therapy should be started immediately. An i.v. bolus dose of 100 U/kg UFH should be followed by a continuous infusion of 1000 U/h to maintain the aPTT at twice normal values.[92,93] Heparin improves oxygenation and hemodynamic status by reducing pulmonary artery obstruction and by preventing further release of vasoactive and bronchoconstrictive mediators from platelets and thrombin, thus decreasing pulmonary vascular resistance.

Vena caval ligation or inferior vena caval filter should be considered in patients on anticoagulation therapy who have recurrent emboli or those who cannot be anticoagulated.[94] Caval ligation has a higher mortality (10–15%) than insertion of a vena caval filter (< 1%) in nonpregnant patients. In 11 cases of temporary inferior vena caval filters inserted prior to delivery, there were no cases of PTE during or after delivery in pregnant women with DVT.[95]

Patients with a massive PTE and acute cardiac decompensation may respond to thrombolytic therapy.[96] Although both urokinase and streptokinase have been used successfully in pregnancy,[97,98] urokinase is considered less antigenic. Recombinant tissue plasminogen activator (rt-PA), has been used successfully in a pregnant patient with massive pulmonary embolism.[99] Use of rt-PA is associated with minimal bleeding complications, as it does not induce systemic fibrinolysis and is active only when it binds to thrombin and is therefore clot specific.[124] Thrombolytic therapy should be monitored by thrombin time, which should not be greater than five times that of normal. Thrombolytic therapy in a pregnant patient is associated with the risk of maternal bleeding and abruptio placentae,[96,97,98,99] and thus should be used cautiously after consultation with a hematologist. Surgical embolectomy is associated with a high mortality rate and therefore should be a last measure in those patients showing rapid clinical deterioration.

Anesthetic management

There are reports of epidural hematoma after anticoagulation and neuraxial blockade[100] and after anticoagulation without neuraxial blockade.[101] Due to the serious consequences of an epidural hematoma, the anesthesiologist should carefully assess the risks versus the benefits of performing regional anesthesia in a patient with coagulopathy.

A regional block should be avoided for either labor analgesia or C/S in patients with an abnormal aPTT. Heparin should be discontinued and aPTT should be normal before elective C/S. In laboring women heparin should be discontinued with the onset of active labor, and i.v. opioid analgesia can be considered in place of epidural analgesia until the aPTT is normal. Protamine may be administered in selected patients who require emergency C/S. Protamine is unpredictable in reversing the anti-Xa activity caused by LMWH.

The American Society of Regional Anesthesia and Pain Medicine (ASRA) has provided guidelines to improve safety of regional anesthesia/analgesia in anticoagulated patients (see Table 1.7 in Chapter 1).[102]

Neuraxial blockade is contraindicated in patients receiving concomitant fibrinolytic therapy, because of the risk of epidural hematoma. All patients who receive regional anesthesia after anticoagulation or fibrinolytic therapy should be followed for signs and symptoms of a developing epidural hematoma – these include severe persistent backache; neurological deficit, including decreased lower limb movement; tenderness over the spinous process; and unexplained fever. Magnetic resonance imaging or CT scan can be useful if the diagnosis of epidural hematoma is in doubt. Early spinal cord decompression reduces the risk of permanent neurological deficits in cases of epidural hematoma.

If C/S is needed in a patient with abnormal coagulation, GA is administered. The risk of GA in the anticoagulated patient includes airway bleeding. There should be a gentle approach to laryngoscopy, tracheal intubation, placement of nasopharyngeal and oral airways, and placement of gastric tubes.

Venous air embolism

Incidence

Venous air embolism is a common occurrence during C/S[103] and vaginal delivery.[104] The incidence of VAE during C/S, as detected by precordial Doppler monitoring, has been reported to be 10–60%.[104,105] Venous air embolism accounts for approximately 1% of all maternal deaths in the United States.

Etiology/pathophysiology

For VAE to occur there must be vascular access and a gradient between the incisional area and the right side of the heart. Subatmospheric venous pressure allows air to be entrained into the venous circulation. A gradient as small as 5 cmH_2O may result in entrainment of large amounts of air. The pressure gradient increases with the height of the venous site above the level of the heart.

The volume and rate of air entrainment and the site of embolization determine the outcome from VAE. Other factors that modify outcome include body position, depth of ventilation, and central venous pressure. Pulmonary edema can develop following VAE, secondary to increased capillary permeability and/or an increase in hydrostatic pulmonary pressure. Hypoxemia invariably occurs in clinically significant air embolism primarily due to increased V/Q mismatching. Hypercarbia can also occur due to an increased alveolar dead space. In humans, large volumes (more than 3 ml/kg) of air may obstruct the pulmonary artery and can be fatal, while smaller amounts may result in a V/Q mismatch, hypoxemia, dysrhythmias, and hypotension. Venous air embolism produces a compensatory increase in minute volume during spontaneous ventilation and may cause a reflex gasp, probably mediated by pulmonary stretch receptors.

The open uterine vessels during C/S allow easy access of air into the venous circulation. The risk of VAE (as suggested by Doppler studies) during C/S, further increases with exteriorization of the uterus. Furthermore, left uterine displacement, use of the Trendelenburg position, and hemorrhage all increase the pressure gradient and thus increase the risk of VAE during C/S. Some investigators have suggested that the incidence of VAE, is reduced to 1% when patients are placed in a five-degree reverse Trendelenburg position during C/S.[104] However, others have failed to demonstrate this benefit.[105]

In paradoxical air embolism (arterial air embolus via a patent foramen ovale or through microvascular intrapulmonary shunts) a small volume of air, as little as 0.025 ml in an animal model,[106] entering the coronary or cerebral circulation can lead to severe cardiovascular and neurological sequelae. Rarely, during the antepartum period, air can be forced through the vagina and travel through the cervical canal to pass beneath the fetal membranes and enter the circulation via subplacental sinuses resulting in severe VAE.[107]

Clinical presentation

Depending on its severity, VAE may go unrecognized or may present with cardiopulmonary dysfunction (Figure 4.4). Chest pain and/or dyspnea can occur in approximately 50% of cases and SaO_2 may fall in 25% of cases. Other physical findings include hypotension, alteration in heart rate (tachycardia and bradycardia), and signs of elevated right-sided pressures. In addition, wheezing and rales due to acute bronchospasm and pulmonary edema may occur. Massive air embolism can present as a sudden, dramatic, and devastating event with hypotension, hypoxemia, and even cardiac arrest.[108]

Diagnosis

The clinical diagnosis of VAE may be difficult because it often mimics other acute cardiopulmonary and cerebrovascular events. Thus, diagnosis of VAE requires a high level of clinical suspicion. Venous air embolism should be suspected when patients complain of chest pain and/or dyspnea, or develop hypotension, low SaO_2, and dysrhythmias.

Electrocardiographic changes during VAE include bradycardia or tachycardia, premature ventricular contractions, heart block, and ST-segment depression. A decrease in SaO_2 and $EtCO_2$ reflect the abnormal V/Q relationship and increased physiological dead space that can result from clinically significant VAE. A rise in

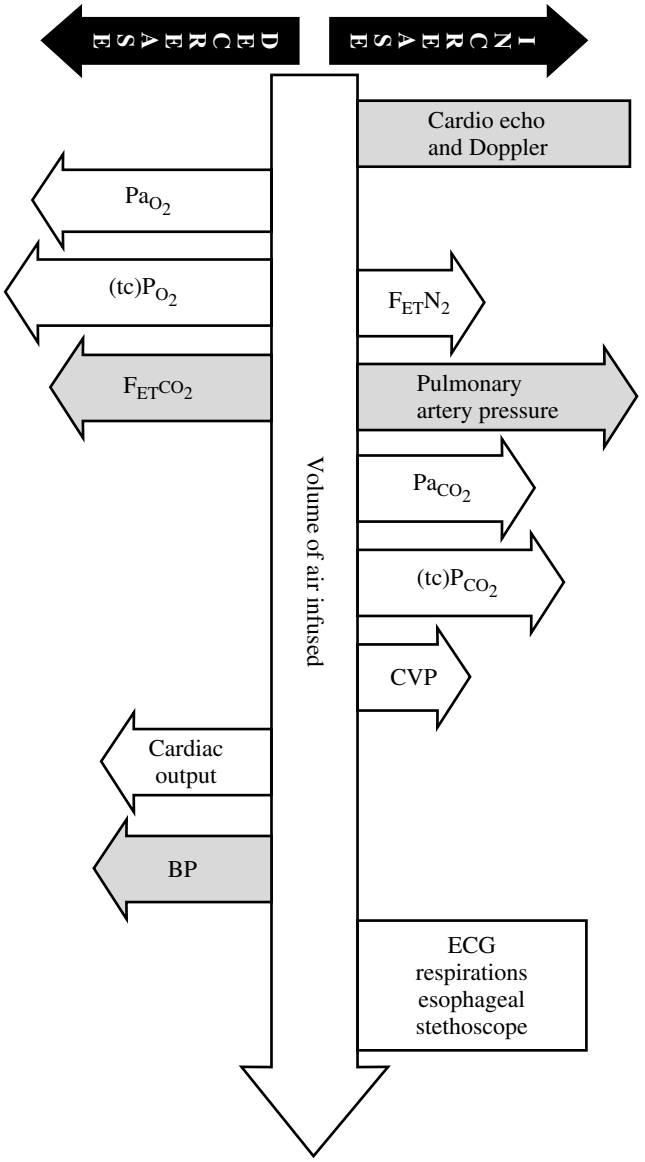


Figure 4.4 Sensitivity of the detection parameters for venous air embolism with increasing air volume (from Black, S. & Cucchiara, R. F. Tumor surgery. In Cucchiara, R. F. & Michenfelder, J. D. (eds.,) *Clinical Neuroanesthesia*. New York: Churchill Livingstone, 1990, p. 285).

end-tidal concentration of nitrogen, as detected by "RASCAL" monitors, is specific for air embolism, as is a transient "mill wheel" murmur, heard during continuous monitoring with an esophageal or precordial stethoscope. This murmur is described as a rhythmic churning sound produced by movement of air bubbles in the RV and is heard throughout the cardiac cycle.

In high-risk patients, such as patients with intracardiac shunts and hypovolemia, precordial Doppler monitoring is recommended. Precordial, low-frequency Doppler is a highly sensitive and readily available method that detects air bubbles as small as 0.1 ml.[109] Transesophageal echocardiography (TEE) is most sensitive in detecting air embolism; however, it requires expensive equipment and interpretation skills. The CXR can demonstrate an air fluid level in the pulmonary vessels and is pathognomonic for VAE.[110] Central venous and pulmonary artery pressures increase and CO decreases with VAE. Abrupt elevations in pulmonary artery pressure (PAP) accompanied by a fall in $EtCO_2$ are indicative of VAE. However, the sensitivity of PAP with respect to VAE is similar to that of the $EtCO_2$. Aspiration of air from the right atrium via the central venous catheter also indicates the occurrence of VAE and may be therapeutic. Arterial blood-gas analysis will often show hypoxemia and hypercarbia.

Table 4.10 Management of venous air embolism during cesarean birth

Flood surgical field with saline
Position patient 5° head-down and left lateral
Discontinue nitrous oxide
Administer 100% oxygen
Support circulation with intravenous volume expansion and vasopressor drugs
Aspirate air through a multiorifice CVP line

Management

The management of VAE includes prevention of further air entrainment by flooding the surgical field with saline and positioning the patient in the left lateral position with five-degree head-down tilt (see Table 4.10). This maneuver places the heart in a dependent position, minimizing the possibility of developing an airlock and improving venous return. Nitrous oxide should be discontinued and 100% O_2 administered. In addition, cardiopulmonary support includes the use of volume expanders and vasopressors. A large multiorifice central venous catheter with the tip placed in the right atrium allows aspiration of air and thus prevents or breaks an airlock. In patients with delayed emergence from anesthesia, CT scan or MRI should be considered to exclude the presence of intracerebral air.

Amniotic fluid embolism

Amniotic fluid embolism (AFE) is a rare but catastrophic complication of pregnancy, which presents with sudden hypoxemia, hypotension, and coagulopathy. The syndrome of AFE was first described in 1926 by Meyer, who reported the presence of constituents of amniotic fluid in the pulmonary vasculature of a young woman who suffered fatal cardiopulmonary collapse during pregnancy.

Incidence

The reported incidence varies from 1 in 8000 to 1 in 80 000 pregnant women. The overall mortality of clinically recognized AFE is reported to be 37–86% with cardiopulmonary collapse occurring in most cases. Approximately 25–50% of patients with AFE die within the first hour of clinical presentation.[111,112]

Table 4.11 Pathophysiology of amniotic fluid embolism

- Mechanical obstruction of pulmonary vasculature by particulate matter:
  - fetal squamous epithelium
  - mucin
  - lanugo hair
- Pulmonary edema due to:
  - alveolar capillary leak
  - microvascular embolic insult
- Left ventricular dysfunction secondary to:
  - arterial hypoxia
  - decreased coronary blood flow
  - circulatory myocardial depressants
- Release of vasoactive substances eliciting a hemodynamic response:
  - pulmonary hypertension
- Anaphylactic shock

Etiology/pathophysiology

Amniotic fluid access to the maternal circulation is essential to the pathogenesis of AFE. The disruption of the integrity of fetal membranes, open uterine or cervical veins, and a concomitant pressure gradient between the amnion and the uterine and cervical veins sufficient to drive the amniotic fluid into the maternal circulation, facilitate amniotic fluid access to the maternal circulation. However, it must be emphasized that there is no correlation between the presence of amniotic fluid in the circulation and the onset of clinical symptoms.[113] In a review of cases reported to the national registry for AFE, the presence of meconium in the amniotic fluid was associated with a poor prognosis, with no neurologically intact survivors.[112] In this report, out of 46 cases of AFE, 30 occurred during labor and 13 occurred after C/S or vaginal delivery. No correlation between hypertonic contractions and the occurrence of amniotic fluid embolism was found, so the authors concluded that uterine hyperstimulation was a result rather than a cause of amniotic fluid embolism.

There are various proposed mechanisms that produce the clinical picture of AFE (see Table 4.11). Pulmonary edema is a common (70%) presentation in humans with AFE, but is absent in primates. Left heart failure is a major physiologic aberration in AFE, but may be preceded by right heart failure. A report of TEE initiated within 15 minutes of the onset of symptoms of a fatal AFE confirmed the occurrence of acute, massive right heart failure and severe pulmonary artery hypertension.[114] The speculation that mechanical obstruction is fundamental to the pathogenesis of AFE has been discounted by autopsy studies that have shown a poor correlation between the amount of particulate matter and clinical findings. Clark and colleagues suggested that the syndrome of AFE is not consistent with an embolic event, and the term "amniotic fluid embolism" should be discarded. This syndrome seems to occur after maternal intravascular exposure to fetal tissue during normal labor, vaginal delivery, or C/S and should be designated in a more descriptive manner as *anaphylactoid syndrome of pregnancy*.[111] Clark and colleagues state that amniotic fluid triggers the release of maternal endogenous mediators, which results in a clinical response similar to both anaphylaxis and septic shock, which suggests a common pathophysiologic mechanism for all of these conditions (see Figure 4.5).

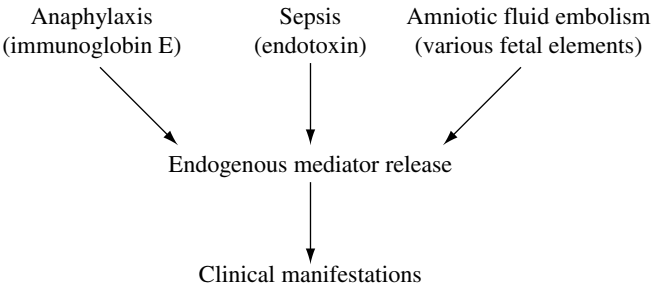


Figure 4.5 Proposed pathological relation between embolism, septic shock, and anaphylactic shock (from Clark, S. L., Hankins, G. D. V., Dudley, D. A. *et al*. Amniotic fluid embolism: analysis of the national registry. *Am. J. Obstet. Gynecol.* 1995; 172: 1158–69).

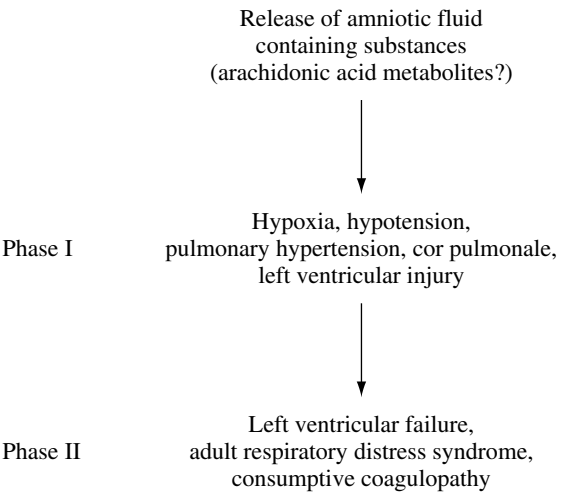


Figure 4.6 Proposed pathophysiology of amniotic fluid embolism (from Clark, S. L. Amniotic fluid embolism. *Crit. Care. Clin.* 1991; 7: 877–82).

The coagulopathy associated with AFE is also incompletely understood. Some in vitro studies have shown that amniotic fluid has a thromboplastin-like quality, which decreases whole blood clotting time, induces platelet aggregation, is associated with the release of platelet factor III and activation of complement and factor X-activating factor.[115,116] In addition, uterine atony caused by the myometrial depressant effect of amniotic fluid may result in massive hemorrhage and contribute to a coagulopathy.

The clinical course of AFE may be attributable to the metabolites of arachidonic acid[117] since the concentration of these metabolites in amniotic fluid increases during labor. The summation of many of these findings led Clark to propose a biphasic model for pathogenesis of AFE that reconciles human and animal data.[111] The model describes the release of amniotic fluid containing vasoactive substances leading to an initial Phase I response, which lasts for 15–30 minutes and involves hypoxemia, dyspnea, pulmonary hypertension, cor pulmonale, and LV injury. A secondary Phase II response includes LV failure, ARDS, and consumptive coagulopathy (see Figure 4.6).

Clinical presentation

Most AFE syndromes have been reported during labor. However, this syndrome has occurred during first and second trimester abortions,[118] and as late as 48 hours postpartum.[119]

The clinical presentation of AFE is generally dramatic, with abrupt onset of hypoxemia (O_2 desaturation), dyspnea, and hypotension with rapid progression to cardiopulmonary arrest. Pulmonary edema has been observed in 24–70% of cases.[119] In 40% of cases, pulmonary edema is followed by varying degrees of consumptive coagulopathy, although coagulopathy may be the presenting manifestation in 10–15% of patients. Central nervous system hypoxia may lead to alterations in mental status with seizures developing in 10–20% of cases. Amniotic fluid embolism may be complicated by myocardial ischemia and infarction, renal failure, liver damage, and neurologic deficits. Superimposed renal failure worsens the prognosis. Occlusion of retinal arterioles by amniotic fluid emboli may occur. These dramatic features may be heralded by nonspecific symptoms of shivering, anxiety, coughing, vomiting, a sensation of bad taste in the mouth, and a sense of impending doom.[119]

Diagnosis

The initial diagnosis is based on the clinical presentation. The definitive diagnosis is made at autopsy with the finding of fetal debris in the maternal pulmonary vasculature, generally in the arterioles and capillaries, but occasionally in the large vessels as well. Routine hematoxylin-eosin staining may be insufficient to demonstrate the fetal elements, and special stains such as acid mucopolysaccharide may be required.

A number of noninvasive methods for the antemortem diagnosis of AFE have been suggested, including the use of an antibody to human keratin, determination of zinc coproporphyrin levels in maternal plasma,[120] and the use of monoclonal antibodies to an amniotic fluid-specific antigen.[121] The sensitivity, specificity, and positive and negative predictive values of these methods of diagnosis remain poorly defined. In addition, there may be no time to perform these tests, due to the catastrophic nature of this syndrome. Electrocardiographic changes include nonspecific ST-segment and T-wave changes, atrial or ventricular rhythm disturbances, RV abnormalities, such as right bundle branch block, right atrial strain, and right axis deviation. Changes on CXR include infiltrates, pleural infusion, atelectasis, or elevation of a hemidiaphragm owing to pneumoconstriction. Arterial blood-gas measurements may show hypoxemia with a mixed metabolic acidosis and respiratory alkalosis. Coagulation abnormalities include decreased fibrinogen and elevated levels of fibrin degradation products (FDP), prolonged PT, aPTT, and thrombocytopenia. Ventilation perfusion scans may be useful to estimate the probability of embolism based on the size of perfusion defect and the presence or absence of matching ventilation scan and CXR abnormalities.

Patients surviving to receive invasive hemodynamic monitoring generally demonstrate LV dysfunction accompanied by moderate or severe elevations in PAOP, PAP, and PVR and depressed LV stroke work index.

The presence of anucleate squamous epithelial cells in the pulmonary microvascular circulation is supportive of AFE. However, this is no longer considered pathognomonic.

Management

Aggressive cardiopulmonary resuscitation (CPR) is imperative due to the catastrophic nature of AFE. Supplemental O_2 should be provided to treat hypoxemia. If this is insufficient, high concentrations of O_2 with continuous positive airway pressure (CPAP) increase functional residual capacity. However, mechanical ventilation is usually necessary because of inadequate maternal PaO_2 and hemodynamic instability. If pulmonary edema ensues, use of PEEP should be considered.

It is important to maintain left uterine displacement to avoid aortocaval compression by the gravid uterus during CPR. If there is no response to advanced CPR within five minutes, C/S should be performed to optimize the outcome for both mother and baby.

Hypotension following AFE should initially be treated with rapid volume administration so as to optimize cardiac preload. In cases of persistent hypotension, fluid administration should be titrated to central venous pressure measurements. Placement of a pulmonary artery catheter is helpful in fluid management and drug therapy in those patients who develop pulmonary edema.

Coagulopathy associated with AFE may be severe but is usually self-limiting. Administration of blood components (fresh-frozen plasma, platelets, packed red blood cells) is often successful. Esposito and colleagues reported the successful use of cardiopulmonary bypass and pulmonary artery embolectomy for treatment of postpartum shock caused by AFE.[122] Amniotic fluid embolism causing intense pulmonary vasoconstriction can be diagnosed with TEE and treated with cardiopulmonary bypass.

Continuous arteriovenous hemofiltration has been used in a patient who developed AFE complicated by renal failure after C/S.[123] Patients who receive regional anesthesia before the onset of AFE should be monitored for the development of an epidural hematoma. Neurologic function should be assessed frequently, as allowed by the physical condition of the patient. The indwelling epidural catheter should preferably be removed as soon as possible but only after correction of the coagulopathy.[124]

Miscellaneous emboli

Fat embolism

Pulmonary fat embolism is a pathological entity characterized by occlusion of pulmonary blood vessels with fat globules that are too large to pass through the capillary bed. The reported incidence of posttraumatic fat embolism syndrome (FES) in the literature ranges from 19–29%,[125,126] with a mortality rate of 10–20%.[127] The prognosis in patients with cerebral manifestations of fat embolism is very poor.

Entry of fat globules into the circulation occurs following skeletal trauma, particularly involving the lower extremity long bones.[128] Fat is detected in pulmonary arterial samples of up to

70% of patients with long-bone and pelvic fractures. Other causes of fat embolism include burns, subcutaneous adipose tissue injury, and acute pancreatitis, sickle-cell crisis during pregnancy, and acute fatty liver of pregnancy.[129,130] The reader is referred to a review of the subject for more details.[131]

Sickle-cell embolism

More than one third of pregnancies in women with sickle-cell syndromes terminate in abortion, stillbirth, or neonatal death.[132] Maternal mortality due to sickle-cell anemia is ~1%, mainly due to pulmonary embolism and infection.[132] In sickle-cell disease erythrocytes undergo sickling when deoxygenated (see Chapter 17). The sickled cells are elongated and crescent shaped and have a tendency to form aggregates. The sickling mainly depends on the presence of abnormal hemoglobin (HbS), which is a hemoglobin variant (valine replaces glutamic acid in the sixth position of the beta-chain). Increased sickling occurs when more than 50% of hemoglobin is HbS. Other factors that affect sickling include vascular stasis, hypothermia, hypovolemia, and acidosis. The sickle cells aggregate in the circulation, which can lead to pulmonary vascular obstruction and pulmonary infarction. Common with other embolic disorders, patients with sickle-cell embolism present with respiratory distress, chest pain, hypoxemia, V/Q mismatch, and pulmonary hypertension. Anesthetic management includes maintenance of oxygenation, avoidance of dehydration, acidosis, and vascular stasis.[133] Avoidance of aortocaval compression is essential even in patients with sickle-cell trait. One patient died from a massive sickle-cell embolus following release of aortocaval compression during C/S at the time of delivery.[134]

Infectious embolism

Infectious emboli may complicate infection anywhere in the body. Even a minor infection may produce a major embolic event. The most common foci are the pelvis, the tricuspid and pulmonic valves, the abdomen, the veins of the extremities, and the skin and subcutaneous tissue. Gram-positive, gram-negative, and anaerobic organisms may be involved and produce somewhat different signs and symptoms. In order for treatment to be successful, the source of infection must be removed.

Summary

Pulmonary embolism should be suspected in a pregnant women presenting with acute cardiopulmonary decompensation. With an increased incidence of DVT in pregnant women, anesthesiologists need to be aware that these patients are prone to PTE. The entrainment of small quantities of air into the vascular compartment is a relatively common occurrence, but only larger volumes of air with sufficiently rapid intravascular entrainment produces clinically detectable effects. Patients undergoing C/S under regional anesthesia, with their uterus exteriorized and who develop hemorrhagic hypovolemia are at a high risk of VAE. Amniotic fluid embolism is usually heralded by a sudden onset of O_2 desaturation, respiratory distress, and cardiovascular collapse. Consumptive coagulopathy and ARDS are the most common complications observed in patients who survive acute AFE. The AFE syndrome seems to occur after maternal intravascular exposure to fetal tissue during normal labor, vaginal delivery, or C/S, and should be designated in a more descriptive manner as *anaphylactoid syndrome of pregnancy*. Early recognition, invasive monitoring, and aggressive management should improve the outcome.

Cystic fibrosis

Epidemiology

Cystic fibrosis (CF) is a lethal genetic disorder with an estimated incidence of 1 in 3300 for Caucasians, 1 in 8500 for Hispanics, 1 in 15 000 for African Americans, and 1 in 32 000 for Asian Americans.[135] In the past, CF was seen rarely during pregnancy but dramatic advances in the management of CF have improved life expectancy and quality of life, so that more women with CF are now becoming pregnant. The number of pregnancies reported to a national CF registry between 1986 and 1990, doubled from 52 to 111.[136]

Pathophysiology

Cystic fibrosis is inherited in an autosomal recessive pattern. The gene responsible for CF is located on the long arm of chromosome 7 that encodes an epithelial cell membrane protein known as the cystic fibrosis transmembrane regulator (CFTR).[137,138] This is a complex chloride channel found in all exocrine tissues.[139]

Mutation of the CFTR gene causes a defect in the CFTR. This results in altered epithelial cell membrane transport of electrolytes in all organs that express CFTR. These include the respiratory, gastrointestinal, and reproductive tracts; the pancreas; and the liver. Defective epithelial transport of electrolytes produces abnormal secretions that result in a multisystem disorder that particularly affects the respiratory and gastrointestinal systems.[139]

More than 1000 mutations have been discovered.[140] The most common mutation results in deletion of phenylalanine at position 508 (ΔF508) of the CFTR. Homozygosity for ΔF508 manifests in one of the most severe forms of CF.[141] Phenotypic expression of CF, however, is variable.[142]

Clinical features

Cystic fibrosis commonly presents as a respiratory disease. Abnormal mucous secretions within the respiratory system result in increased adhesiveness of, and difficulty in clearing, secretions, which then cause small airways obstruction. Chronic airway obstruction and mucus retention lead to airway colonization and chronic infection, the most common pathogen being *Pseudomonas aeruginosa*. The chronic inflammation that ensues causes progressive tissue damage and subsequent fibrosis, bronchiectasis, and distal hyperinflation. This, together with

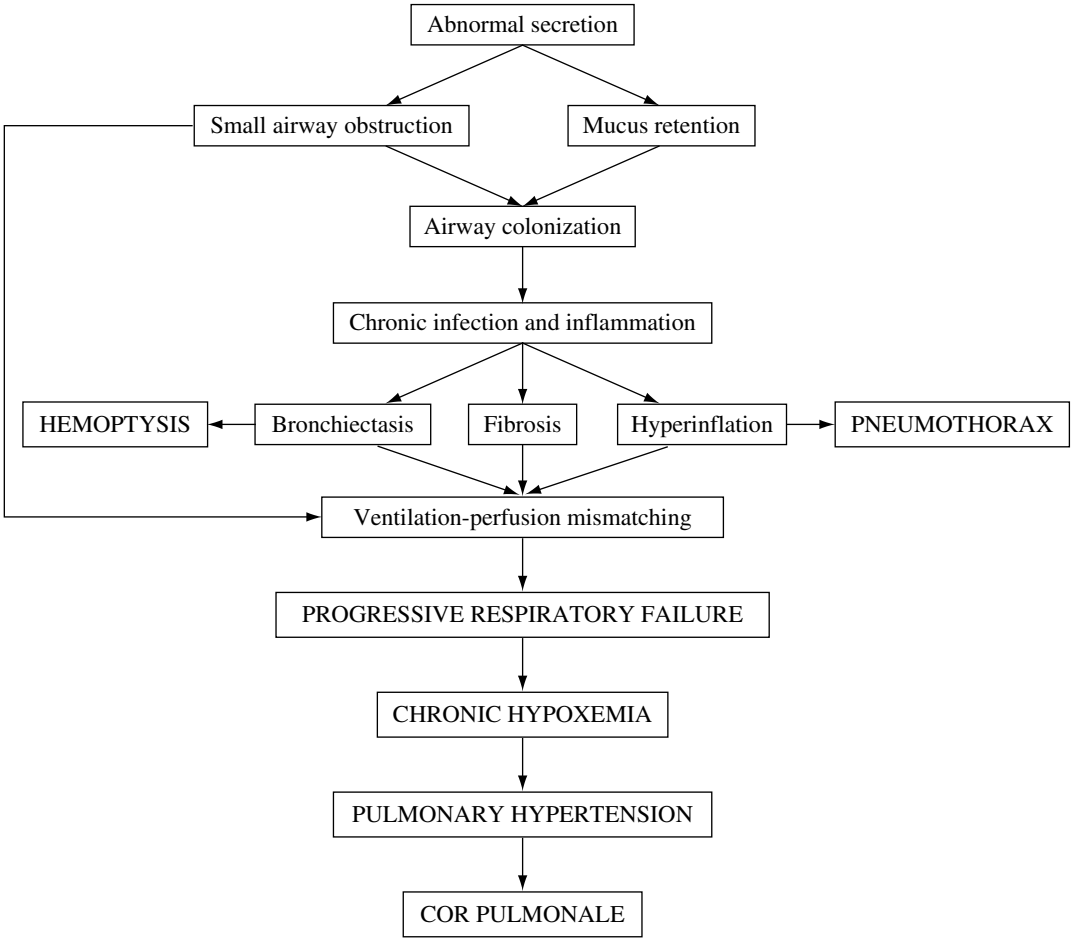


Figure 4.7 Cardiorespiratory effects of cystic fibrosis.

small airway obstruction, gives rise to V/Q mismatching, which can lead to hypoxemia (see Figure 4.7).

Respiratory manifestations of CF usually start with a recurrent cough that gradually becomes persistent and productive. Over time airway hyperactivity becomes a common finding and pulmonary function testing reveals an obstructive pattern. With advanced disease progressive respiratory failure occurs. Lung hyperinflation predisposes to spontaneous pneumothorax and bronchiectasis causes hemoptysis, which can be massive. Pulmonary hypertension secondary to chronic hypoxemia and subsequent RV dysfunction (cor pulmonale) appear as late sequelae (see Figure 4.1).

Exocrine gland dysfunction involving the pancreas is common and leads to maldigestion, malabsorption, and insulin-dependent diabetes mellitus. Subacute intestinal obstruction can also occur.[143,144] In late disease, biliary cirrhosis and portal hypertension may occur, with abnormalities of hepatic function, hypoalbuminemia, and jaundice.

Abnormal cervical mucous production leads to female subfertility. In the male, obstructive azoospermia involving the vas deferens is a frequent cause of infertility.

Diagnosis

The clinical diagnosis of CF is based on the presence of chronic obstructive lung disease before age 20, exocrine pancreatic insufficiency, and a family history of CF. Laboratory measurements of sweat chloride concentrations greater than 60 mEq/l assist with the diagnosis. DNA testing to isolate the specific gene mutation confirms the diagnosis.

Treatment

Respiratory management of CF is primarily symptomatic, with postural drainage for patients with copious mucus production,[145] and bronchodilators for those with a reversible component of airway obstruction.[146] Mild infectious exacerbations may be treated with oral antibiotics. Inhaled tobramycin and colistin have been used to manage respiratory infections with *Pseudomonas aeruginosa*,[147] and may be added to oral antibiotic treatment of milder infectious exacerbations. However, a severe acute respiratory infection warrants immediate hospitalization and aggressive therapy with i.v. antibiotics.[148] It is common practice to administer antibiotics continuously in order to prevent recurrence, but there are insufficient data to support this practice. Patients with chronic hypoxemia and cor pulmonale may benefit from continuous O_2 therapy.

Other forms of therapy include inhaled recombinant human deoxyribonucleases to reduce sputum viscosity,[149,150] lung transplantation (for patients with end-stage disease),[151,152,153] and gene therapy.[154] Current approaches to gene therapy include

the transfer of the normal CFTR gene to airway epithelium using viral or nonviral carriers.[154,155,156]

Maintenance of adequate nutritional intake is important in the management of patients with CF. Pancreatic insufficiency requires replacement therapy with lipase, protease, and amylase enzymes to prevent malabsorption.

Cystic fibrosis and pregnancy

Effect of pregnancy on cystic fibrosis

A 1980 report by Cohen and colleagues[157] found that 18% of pregnant women with CF died within two years of delivery. More recent reports indicate that pregnancy does not affect CF. McMullen and colleagues found that, over the same time period, women with CF who became pregnant experienced similar respiratory and health trends as nonpregnant CF women. However, pregnant women used a greater number of therapies and received more intense monitoring of their health.[158] Geddes emphasized that lung function appears to be the most significant determining factor of outcome in pregnant women with CF.[159] FEV_1 decreases similarly in both nonpregnant CF women and pregnant CF women.[158]

Effect of cystic fibrosis on pregnancy

Preterm labor is markedly increased (as high as 45%) in mothers with CF,[159,160,161,162] possibly due to poor maternal nutrition and chronic hypoxemia. Preterm labor most commonly occurs in mothers with severe disease. Edenborough and colleagues[163,164] reported a substantial risk of preterm delivery in women with a prepregnancy FEV_1 of less than 60% of predicted. Because of the increased rate of preterm delivery, the perinatal mortality rate is also high.[164]

Antepartum management

Patients should be reviewed throughout pregnancy by a multidisciplinary team, which includes the pulmonologist, obstetrician, physiotherapist, nutritionist, and anesthesiologist. Involvement of an anesthesiologist should not be confined to the peripartum period. Regular assessment of the cardiorespiratory system detects deterioration resulting from the changing demands of pregnancy. Good bronchial toilet, early involvement of physiotherapy, maintenance of CF medications, and vigorous treatment of respiratory infections are mandatory.

It is important to assess and maintain optimal nutritional status during pregnancy, which may necessitate enteral feeding. Pancreatic function should be evaluated, pancreatic enzyme supplementation maintained, and diabetes mellitus closely controlled. One study has shown that pregnant CF women have decreased insulin sensitivity and a predisposition to early development of diabetes and poor weight gain.[165]

Venous access may be difficult if there have been multiple admissions to hospital for parenteral therapy, and a long-term subcutaneous infusion device may be helpful (see Table 4.12).

Table 4.12 Intrapartum and regional anesthetic management for parturient with cystic fibrosis

Discuss with multidisciplinary team (includes obstetric and nursing teams)
Ensure good intravenous access
Continue all cystic fibrosis medications
Continue active physiotherapy
In patients with diabetes mellitus, check blood glucose regularly and maintain tight control
Avoid dehydration
Monitor SaO_2 and administer humidified oxygen as indicated
Establish labor epidural analgesia early, using a weak bupivacaine solution with opioid supplementation, and dose slowly and incrementally aiming for a T8 upper sensory level
Employ elective assisted delivery to minimize cardiorespiratory stress
Use epidural anesthesia for cesarean section, if possible, and dose slowly and incrementally aiming for a T6 upper sensory level

Intrapartum management

General principles of management

Discussion among the pulmonologist, obstetrician, and anesthesiologist allows early formulation of a labor and delivery plan that is based on the severity of the disease, obstetric indications, and the patient's wishes. Preanesthetic assessment of the patient should be made at an early stage. The parturient should be carefully assessed with particular reference to her pulmonary condition, nutritional status, and diagnostic investigations. Options for labor analgesia and C/S should be addressed early.

Continuous SaO_2 monitoring should be established, and humidified O_2 administered if the SaO_2 falls below 94%. Direct arterial pressure monitoring is useful if cardiorespiratory function deteriorates. Cor pulmonale can be confirmed by echocardiography. Central venous pressure plus pulmonary artery monitoring is indicated when pulmonary hypertension or heart failure is suspected.

Other factors to consider during the peripartum period include maintenance of hydration, continuation of CF medications, and monitoring insulin requirements in those women with diabetes mellitus.

Valsalva maneuvers in the second stage risk a pneumothorax in women with CF, so assisted delivery reduces the cardiorespiratory demands of delivery and the risk of pneumothorax. Deterioration in maternal or fetal status may require rapid delivery by C/S.

Anesthetic management during labor

Considerations regarding anesthetic management center on maintaining optimal cardiorespiratory function. Adequate pain relief during labor prevents hyperventilation associated with labor pain. Hyperventilation increases work of breathing and may cause decompensation in women with severe pulmonary dysfunction.

Nitrous oxide for analgesia is not recommended given the increased risk of barotrauma due to air trapping. Parenteral opioid analgesia may worsen pulmonary function by depressing

respiratory drive and inhibiting cough. Intrathecal opioids have been used for first stage of labor,[166] but patients should be monitored for respiratory depression. Pain in the second stage can be more difficult to control and may require the use of local anesthetic nerve blocks.

Continuous lumbar epidural analgesia can provide excellent pain relief and has been used in women with CF.[167,168,169] A high thoracic motor block, which may impair the parturient's ability to cough and eliminate thick secretions, must be avoided. Use of dilute solutions of bupivacaine with opioid supplementation, and slow, incremental administration will keep the upper sensory level below T8. When there is evidence of heart failure, fluids should be administered carefully with CVP/PCWP monitoring.

Anesthetic management for cesarean section

In parturients with CF, no differences in outcome have been documented between general and regional anesthesia for C/S. The choice between general or regional techniques should be made on the basis of individual circumstances, taking into account the risks and benefits of each technique. When there is evidence of heart failure, fluid administration should be titrated against the central venous pressure.

Endotracheal intubation with GA may provoke bronchospasm, and positive pressure ventilation may lead to barotrauma. If GA is elected, the following should be considered: (1) the patient should receive 100% O_2 prior to intubation for a longer period of time to produce effective denitrogenation; (2) employ techniques to reduce the risk of bronchospasm during endotracheal intubation; (3) humidify anesthetic gases to prevent inspissation of mucus; (4) use positive-pressure ventilation with adequate tidal volumes and frequent suctioning to minimize the risk of atelectasis and collapse; (5) adjust ventilator settings to allow an appropriately long expiratory phase to prevent air trapping and reduce the risk of barotrauma; (6) maintain oxygenation with an adequate inspired O_2 concentration and avoid nitrous oxide because of the risk of air trapping (see Table 4.13).

Regional anesthesia offers the advantage of avoiding endotracheal intubation with its associated risks. However, a high thoracic motor block, which may impair ventilation and the ability to cough, must be avoided. This can be achieved by using a continuous catheter technique to titrate epidural or spinal agents, and by slow, incremental administration of local anesthetic solution. It is prudent to aim for an upper sensory level of T6 to lessen the risk of respiratory embarrassment. Using this approach the successful administration of epidural anesthesia in a parturient with CF has been reported.[170] Some patients may not tolerate lying flat, in which case regional anesthesia is best avoided.

Single-shot spinal anesthesia produces a dense motor and sensory block that is difficult to control and is of very rapid onset. In the patient with more severe respiratory disease, this sudden high block may precipitate a respiratory crisis. For these reasons this technique is not recommended. A CSE technique with a low intrathecal dose may be a suitable alternative.

Following C/S, these patients require close attention to ensure stability of hemodynamic and pulmonary function. An early return to full mobility should be encouraged and adequate pain relief is important in achieving this. Postoperative analgesia can be achieved with parenteral or neuraxial techniques in conjunction with NSAID therapy. Clinical respiratory status must be monitored regularly to detect opioid-induced respiratory depression.

Table 4.13 General anesthetic management for parturient with cystic fibrosis

Preoxygenate with 100% for a longer period of time to produce effective denitrogenation
Humidify anesthetic gases to prevent inspissation of mucus
Employ techniques to reduce the risk of bronchospasm during endotracheal intubation
Institute positive pressure ventilation with adequate tidal volumes and frequent suctioning to minimize the risk of atelectasis and collapse
Adjust ventilator settings to allow for an appropriately long expiratory phase to prevent air trapping and reduce the risk of barotrauma
Maintain oxygenation with an adequate inspired oxygen concentration
Avoid nitrous oxide because of the possibility of air trapping

Summary

Cystic fibrosis is a rare inherited disorder, which can coexist with pregnancy. Abnormal mucous secretions within the respiratory system may lead to difficulty in clearing secretions and small airways obstruction. Respiratory management of CF includes postural drainage and bronchodilators. Recent reports indicate that pregnancy per se does not affect CF; however, the incidence of preterm labor is increased in mothers with CF. Women with CF should be managed by a multidisciplinary team, and a plan for labor and delivery should be based on the severity of the disease. Continuous lumbar epidural analgesia has been used successfully in women with CF and no differences in outcome have been documented between general and regional anesthesia for C/S. The choice between general or regional techniques should be made on an individual basis, taking into account the risks and benefits of both techniques.

Pneumothorax

Introduction

Pneumothorax is rare in pregnancy and about 50% of cases are secondary to identifiable risk factors (see Table 4.14). Primary pneumothorax (PP) occurs in the absence of an identifiable risk factor. However, PP may occur in women with unrecognized lung disease, as evidenced by CT studies. In these patients, pneumothorax probably results from rupture of subpleural blebs,[171] especially with the increased respiratory demands of pregnancy. Pneumothorax can occur at any time during pregnancy, although half occur during the first and second trimesters while the remainder occur during the third trimester.[172]

Table 4.14 Causes of secondary pneumothorax

Respiratory tract infection
Asthma
Prior history of pneumothorax
Cocaine abuse
Hyperemesis gravidarum
Histoplasmosis
Tuberculosis
Lymphangiomyomatosis
Alpha$_1$ antitrypsin deficiency
Chest trauma
Iatrogenic

Clinical features

Patients usually complain of a sudden onset dyspnea and pleuritic chest pain. The severity of symptoms is primarily related to the volume of air in the pleural space, with dyspnea being more prominent if the pneumothorax is large. A large pneumothorax is associated with tachypnea, tachycardia, ipsilateral diminished breath sounds with hyperresonant percussion, and hypoxemia. When hypotension is present, tension pneumothorax must be considered. Reliance on classic clinical findings, however, may lead to misdiagnosis. Chest pain and dyspnea may be attributed erroneously to other causes.

Definitive diagnosis is by chest x-ray. The fetus is not at substantial risk from radiation when a chest x-ray is performed with the maternal abdomen shielded. The estimated dose of radiation to the uterus in this setting is 1 mrad per examination.

Acute management of pneumothorax

Maternal O_2 consumption is increased 20% during pregnancy. Any additional respiratory stress may rapidly induce hypoxemia, which can jeopardize the fetus.[173] Therefore, all pregnant patients with pneumothorax should be hospitalized regardless of the size of the pneumothorax, and oxygen administered while continuously monitoring O_2 saturation.

Treatment criteria for the management of pneumothorax in pregnant patients are similar to those for nonpregnant patients. For unstable patients, (e.g. women with tension pneumothorax and hemodynamic compromise), immediate tube thoracostomy is necessary (see Figure 4.8). Needle aspiration may precede tube thoracostomy as a life-saving measure.[174] A stable pneumothorax, which occupies less than 15% of the hemithorax, can be managed with observation and administration of supplemental O_2 (see Figure 4.8). The rate of air reabsorption is markedly increased with supplemental O_2.

For patients with stable PP greater than 15%, catheter aspiration will suffice since both aspiration and tube thoracostomy have been associated with similar rates of success and recurrence (see Figure 4.8).[174,175] Catheter aspiration is typically accomplished by passing an 8-French catheter into the pleural space over an 18-gauge needle. Following an adequate period of observation and radiographic confirmation of lung expansion the patient can be discharged from hospital. If a leak persists despite aspiration, tube thoracostomy should be performed. Women with failed tube thoracostomy, or those with recurrent PP following successful aspiration or tube thoracostomy, should receive definitive treatment using thoracoscopy, bleb resection, and pleurodesis (see Figure 4.8). Thoracoscopy is effective in the prevention of recurrence.[176]

For patients with stable secondary pneumothorax >15%, initial treatment consists of tube thoracostomy since aspiration is less likely to be successful. Definitive therapy using thoracoscopy with bleb resection and pleurodesis is then performed to prevent recurrence. Thoracoscopy with bleb resection and pleurodesis is also indicated for failed tube thoracostomy.

Thoracotomy with bleb resection and pleurodesis has been the traditional approach to definitive treatment; however, thoracotomy confers maternal and fetal risks of major surgery, significant postoperative pain, prolonged recovery,[176] and greater mortality. Consequently, thoracoscopy is increasingly replacing thoracotomy for definitive treatment, and has successfully been used in pregnant patients with pneumothorax.[177,178]

For persistent or recurrent pneumothorax during pregnancy, some have advocated conservative management using long-term chest drainage, while delaying definitive treatment until after delivery.[179] However, long-term chest drainage predisposes to empyema, pain, and immobility.

Intrapartum management of pneumothorax

Oxygen consumption is increased 50% during labor. If a parturient presents with pneumothorax during the intrapartum period, the additional respiratory stress can readily lead to hypoxemia and risk fetal compromise. Therefore, O_2 is administered while O_2 saturation is continuously monitored, and treatment of the acute episode is as described earlier.

Epidural analgesia is highly recommended at an early stage in labor because it dramatically reduces maternal O_2 demand and can be used for C/S if the need arises. For a vaginal delivery, an elective assisted delivery is recommended. One wants to avoid having the woman push, because increased intrathoracic pressure from expulsive efforts can aggravate the pneumothorax. For C/S, regional anesthesia is highly desirable and GA should be avoided, if possible. When GA is unavoidable, increased minute volumes may be required to maintain adequate ventilation in the presence of a continued leak when a thoracotomy tube is present. Airway pressures should be kept as low as possible to minimize air leak, and nitrous oxide should be avoided.

Labor epidural analgesia and assisted delivery are recommended for patients with an antepartum history of pneumothorax who have not received definitive surgical therapy, since expulsive efforts during the second stage of labor can lead to recurrence.[178,179] In such patients, regional anesthesia is recommended for C/S. If GA is unavoidable, similar precautions are taken as previously outlined.

Patients with definitive surgical therapy during pregnancy may be allowed to attempt spontaneous vaginal delivery. Again, regional anesthesia for C/S is preferable in these women, although, if required, GA can be administered safely.

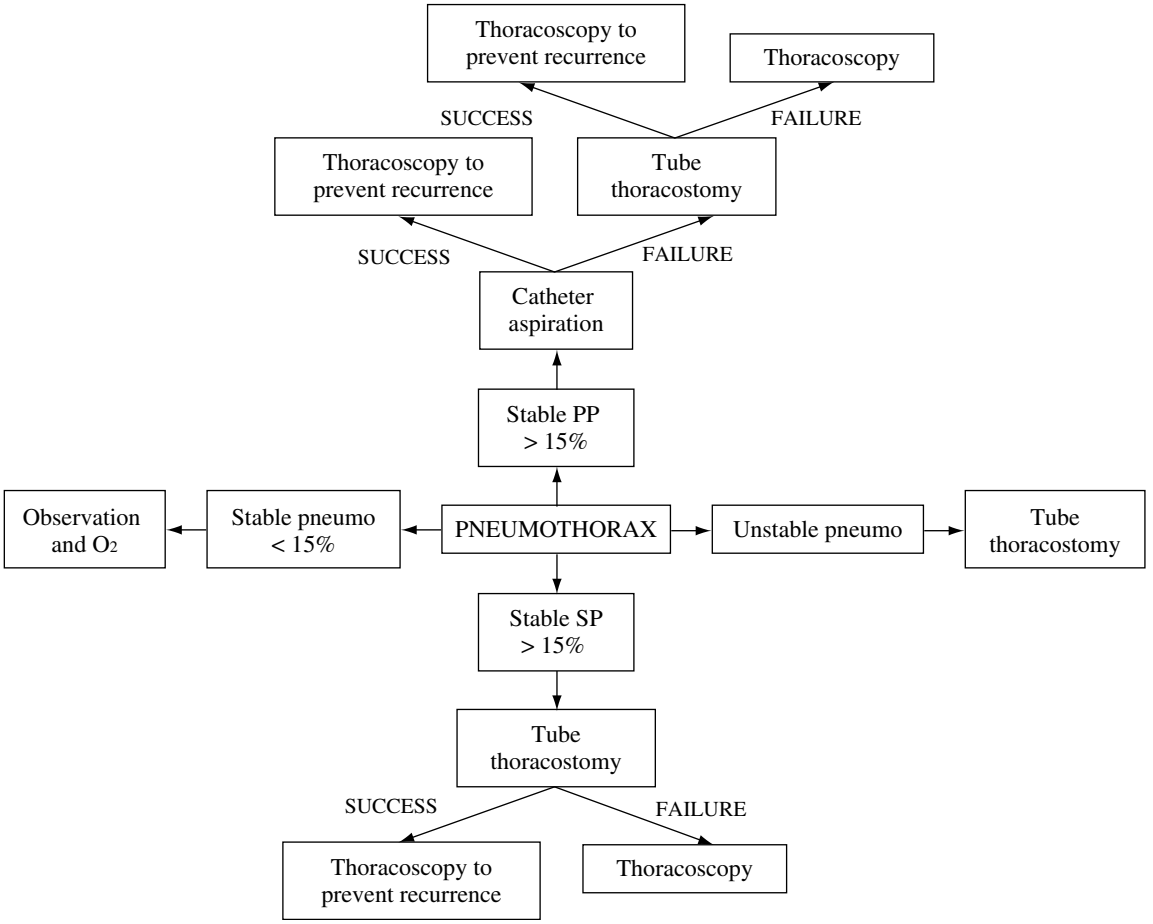


Figure 4.8 Acute management of pneumothorax.

Miscellaneous respiratory disorders

Tracheal stenosis

Tracheal stenosis can be idiopathic or secondary to previous trauma. In nonpregnant patients, signs of upper airway obstruction are absent until 75% narrowing occurs. However, during pregnancy, airway engorgement can increase the severity of preexisting tracheal stenosis.[180] Parturients with uncorrected stenosis will not tolerate the increased ventilatory demands of labor. Sutcliffe *et al.* described a patient with uncorrected tracheal stenosis who underwent uneventful C/S under regional anesthesia but died postpartum from airway obstruction.[181]

Management options for tracheal stenosis include balloon dilation, tracheal stenting, laser excision, or tracheal resection with reconstruction.[182] Persistent obstruction despite the aforementioned interventional methods may warrant tracheostomy. Regional anesthesia avoids instrumentation of the trachea and has been utilized for labor analgesia.[180] Mask-inhalation induction with sevoflurane has been used for operative delivery in a parturient with tracheal stenosis.[183]

Congenital central hypoventilation syndrome

Congenital central hypoventilation syndrome (CCHS) stems from failure of autonomic control of breathing and manifests with hypoventilation and hypoxia primarily during sleep.[184] These patients have negligible or absent ventilatory sensitivity to hypoxia and hypercapnia.[185] If left untreated, chronic hypoxia can lead to pulmonary hypertension and, eventually, cor pulmonale. Although the etiology is unknown, there is considerable evidence to support a genetic mechanism.[186,187] The diagnosis of CCHS is one of exclusion. Most patients require lifelong ventilatory support during sleep, while a few patients require such support 24 hours a day. Options for ventilatory support include positive-pressure ventilation via tracheostomy, positive-pressure ventilation via nasal or face mask, bilevel positive airway pressure (BiPAP), or diaphragmatic pacing.[184]

Endogenous progesterone levels are raised during pregnancy. Although progesterone is a respiratory stimulant that increases central chemoreceptor sensitivity, no improvement in ventilatory response to hypercapnia has been demonstrated during pregnancy.[188] Of all the options for ventilatory support, diaphragmatic pacing has been used successfully during pregnancy, despite the potential for diaphragmatic impairment from uterine growth. However, parturients must be closely monitored with regular polysomnograms to assess the need for adjustments in pacer settings.

The use of epidural anesthesia for C/S has been described in parturients with CCHS treated with diaphragmatic pacing. In such patients, all central nervous system depressants must be avoided. Furthermore, following C/S, incisional pain often prevents the use

of diaphragmatic pacing during which time BiPAP ventilation is utilized until diaphragmatic pacing can be resumed.

Pulmonary lymphangioleiomyomatosis

Pulmonary lymphangioleiomyomatosis (LAM) is characterized by the hamartomatous proliferation of smooth muscle of the pulmonary bronchioles, arterioles, and lymphatic vessels resulting in cystic degeneration of lung tissue with variable progressive loss of pulmonary function.[189] Rupture of peripheral lung cysts can lead to pneumothorax, which is a common presenting feature.[190] Disruption of pulmonary lymph drainage can lead to chylous pleural effusions. Extrathoracic manifestations include chylous ascites; hepatic and renal angiomyolipomas; and uterine leiomyomas.[191,192]

There is no curative treatment for this condition, although hormonal therapy appears promising.[193] Supportive therapy includes standard treatments for obstructive lung disease and pneumothorax. Advanced disease may require lung transplantation.[194] A small pneumothorax can be managed conservatively but there is the risk for recurrence. A large or symptomatic pneumothorax requires intercostal drainage followed by definitive therapy (see earlier).

Epidural analgesia should be utilized during labor to minimize fluctuations in intrathoracic pressure during painful contractions and to facilitate emergency C/S without the need for GA.[189] Assisted vaginal delivery is preferable to avoid high intrapleural pressures associated with pushing, especially in parturients with a history of surgically untreated pneumothorax. Regional anesthesia has been used successfully for C/S in parturients with LAM.[189] General anesthesia has been used for emergency C/S and in these situations it is advisable to avoid nitrous oxide.

Interstitial lung disease

Interstitial lung disease (ILD) is characterized by varying degrees of inflammation and fibrosis resulting in loss of alveolar-capillary units and lung volumes, with subsequent development of chronic hypoxemia and pulmonary hypertension. A variety of disorders can result in ILD and these include idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, drug-induced alveolitis, and connective tissue disorders.[195] During pregnancy, basal atelectasis from the elevated diaphragm and increased O_2 consumption increase V/Q mismatching and can worsen hypoxemia.

Management of parturients with ILD includes baseline pulmonary function testing; careful monitoring; and aggressive treatment of underlying disease and superimposed infections. Central hemodynamic monitoring should be reserved to optimize fluid management and to monitor cardiac function in those with significant pulmonary hypertension and for those with severe hypoxemia. Anesthetic management should emphasize pain management in order to reduce O_2 consumption, and this is achieved with neuraxial anesthesia. Neuraxial anesthesia has been used successfully for labor analgesia and C/S in women with ILD.[195] General anesthesia can be associated with prolonged postoperative mechanical ventilation.

Summary

Respiratory disorders in pregnancy have the potential to worsen with the physiologic and hormonal stresses that occur. It is important for obstetric anesthesiologists to see these women early in pregnancy and to review any special investigations that have been performed. Timely consultation with pulmonologists and perinatologists is important in providing the best anesthetic care to pregnant women with pulmonary disease.

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5 MYOPATHIES

Chantal Crochetiere

Introduction

Myopathies are diseases of the skeletal muscle cell with intact innervation.[1] The hereditary myopathies are the muscular dystrophies, congenital myopathies, metabolic myopathies, inflammatory myopathies, and disorders of muscle membrane excitability. Pregnant women with a myopathy have specific needs depending on the symptoms and severity of the disease. Exacerbation of muscle weakness is common, especially in the third trimester. This decreased muscle strength may not be able to compensate for the high demands of labor and delivery. Pregnancy may occasionally uncover a disease that was previously asymptomatic. Multidisciplinary consultation early in the pregnancy is important for a successful outcome.

Hereditary myopathies (see Table 5.1)

Muscular dystrophy

Muscular dystrophy is a major cause of progressive weakness and wasting of the musculature of the limbs and trunk. It usually can be differentiated from a neuropathy by the involvement of the proximal muscle, the absence of sensory disturbances, and abnormalities of the electromyogram, muscle biopsy, and DNA studies. Muscular dystrophies are the result of a primary genetic defect, which is specific to each type. Inheritance is due to a dominant, a recessive, or a sex-linked gene, or a muscular dystrophy may arise by the occurrence of a mutation. Classification is based on historic descriptions or clinical similarities. Since oculopharyngeal dystrophy has an onset in the fifth or sixth decade it will not be discussed here.

Duchenne, Becker, and Emery-Dreifuss muscular dystrophies

Duchenne, Becker, and Emery-Dreifuss muscular dystrophies are sex-linked disorders affecting males and they are now classified as dystrophinopathies. These three diseases are amenable to carrier detection and prenatal diagnosis by DNA analysis. Female carriers usually show no clinical signs but on occasion may manifest minor features or even slight or more severe degrees of weakness.[2,3,4] In a series of 56 carriers of Duchenne or Becker dystrophy, most were asymptomatic but 18% had cardiac abnormalities. Most of those with cardiac abnormalities showed only borderline abnormalities and the majority were older (>45 years). Echocardiography was abnormal more frequently than electrocardiogram (EKG). The prevalence of skeletal-muscle weakness in the same series was 12%.[5]

In conclusion, it is important to realize that there is no apparent correlation between the presence of skeletal-muscle involvement and cardiac abnormalities. It is recommended that all carriers have ECG and echocardiography every five years. Symptomatic female carriers for Duchenne may be difficult to distinguish clinically from limb-girdle muscular dystrophy.[6] Female carriers of Emery-Dreifuss muscular dystrophy without muscular involvement may also experience cardiac impairment (conduction defects or cardiomyopathy)[7] and a pacemaker may be lifesaving.[1]

Myotonic dystrophy (dystrophica myotonia = myotonia atrophica = Steinert myopathy)

Myotonic dystrophy is the most frequent inherited muscular disorder among adults,[8] the incidence of the gene is 13.5:100 000 and the prevalence of the disease is 5:100 000.[9] It is an autosomal dominant transmitted disease with variable expression. Although myotonic dystrophy usually begins in early adult life, a congenital form is described. Prevalence is equal between the sexes, but pathological changes may be more obvious in males.[10]

Progressive distal-limb muscle weakness and wasting, failure of muscles to relax after a forceful contraction (myotonic handshake) and weakness of facial muscles[11] are the major distinguishing features. Myotonia is the most common finding on physical examination but is often a relatively insignificant component in relation to other features of the syndrome. Percussion myotonia may be present when the grasp response is not found. Severe atrophy of the temporalis and sternocleidomastoid muscles appears early and leads to typical facies.[12] Diagnosis is made by family history and physical examination, and confirmed by electromyography and muscle biopsy. Myotonic dystrophy is a multisystem disease (see Table 5.2) and involves smooth as well as striated muscle.[7,13,14] It is divided in two subgroups: Type 1 and Type 2. Myotonic dystrophy Type 2 is clinically similar to Type 1 (myotonia, distal weakness, frontal baldness, cataracts, infertility, and cardiac dysrhythmia) but less severe (less dementia, hypersomnia, and diabetes).[15]

Myotonic dystrophy and pregnancy Many case reports of myotonic dystrophy during pregnancy have been described.[11,12,16,17,18,19,20,21] Fertility in women with myotonic dystrophy is not reduced except in those severely affected.[22] Pregnancy does not usually affect the long-term course of the disease.[23] Temporary exacerbation of myotonia and muscle weakness may occur during the third trimester[11] with rapid improvement after delivery. Deterioration may be related to progesterone levels[24] or may be attributed partly to inactivity.[11] In many women, symptoms are first noticed during pregnancy,[24] or the disease may be diagnosed for the first time after the birth of a child affected with the congenital form.[12,24]

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Table 5.1 Hereditary myopathies[1]

1. **Muscular dystrophy**
   - Myotonic
   - Facioscapulohumeral
   - Limb-girdle
   - Scapuloperoneal
   - Congenital
2. **Congenital myopathies**
   - Central core
   - Mini core
   - Nemaline
   - Myotubular
   - King-Denborough
3. **Metabolic myopathies** (disorders of muscle energy metabolism)
   - Glycogen storage and glycolytic defects
   - Disorders of lipid metabolism
4. **Disorders of muscle membrane excitability**
   - Calcium channel disorders of muscle (hypokalemic periodic paralysis)
   - Sodium channel disorders of muscle
   - Hyperkalemic periodic paralysis
   - Paramyotonia congenita
   - Potassium aggravated myotonia (sodium channel myotonia)
   - Chloride channel disorders of muscle (myotonia congenita)

Table 5.2 Clinical features of myotonic dystrophy

- Mild mental retardation
- Alopecia
- Blepharo-conjunctivitis
- Cataract (presenile)
- Nasal voice
- Dysarthria
- Respiratory system:
  - atrophy of respiratory muscles
  - central sleep apnea[7]
  - aspiration pneumonia
- Cardiac system:
  - cardiac conduction defects
  - atrial dysrhythmias
  - relative hypotension[13]
  - cardiomyopathy
- Digestive system:
  - abnormal swallowing
  - incoordination of upper esophageal sphincter
  - decreased tone in the lower esophageal sphincter
  - dilated stomach and delayed gastric emptying
  - intestinal pseudo-obstruction[14]
- Endocrine system:
  - abnormalities of glucose metabolism
  - gonadal atrophy in males

Table 5.3 Myotonic dystrophy – obstetrical complications

- Spontaneous abortion
- Polyhydramnios
- Premature labor
- Abnormal presentation
- Cesarean delivery
- Prolonged first stage (?)
- Inability to bear down
- Uterine atony
- Retained placenta
- Placenta previa and accreta
- Increased incidence of neonatal death

Some authors[25] have described inadequate uterine contractions in the first stage of labor while others[20,24] observed a normal or shorter course of labor with the usual response to oxytocin. The parturient with myotonic dystrophy has a high incidence of obstetrical complications that may require anesthetic assistance (see Table 5.3).

Premature labor, with or without polyhydramnios, is common. Prolongation of pregnancy in these women is important from the fetal point of view, since most preterm babies with congenital myotonic dystrophy require ventilatory support whereas term babies are less affected (50% require ventilation).[26] Tocolytic therapy may delay delivery for 24 to 48 hours, which allows administration of a glucocorticoid to accelerate fetal lung maturity. Nifedipine appears to be more effective than ritodrine as a tocolytic agent and has a lower incidence of adverse hemodynamic and metabolic changes, so is now the first-line tocolytic agent.[27] Nifedipine is a potent smooth-muscle dilator and unlike verapamil has little negative inotropic effect.[28] Calcium channel blocking drugs decrease anesthetic requirements by 25%.[29] Verapamil has precipitated respiratory failure in a patient with Duchenne muscular dystrophy.[30] Skeletal-muscle weakness is listed as a less common side effect of nifedipine.[28]

In cases of premature labor, bed rest, hydration, indomethacin, and possibly epidural analgesia should be tried first. If needed, the smallest dose of nifedipine should be used with caution under ECG monitoring and muscle-strength evaluation. If the patient requires general anesthesia, all anesthetic drugs should be carefully titrated.

Preeclampsia in myotonic dystrophy has been reported.[12] Magnesium sulfate ($MgSO_4$) may increase muscular weakness in patients with this disorder. Those who require $MgSO_4$ should be examined frequently and the $MgSO_4$ infusion maintained to provide the lowest therapeutic serum level in order to avoid respiratory compromise.

Congenital myotonic dystrophy Congenital myotonic dystrophy is the most severe form of the disease and it has a high mortality rate.[31] It is transmitted solely by an affected mother[32] who may be asymptomatic.[22] The risk of having an affected child with the congenital form is 10%, increasing to 40% if a previous child was affected.[33] Older women have more severely affected children.[34]

The most characteristic symptoms during pregnancy are reduced fetal movements and polyhydramnios, caused by impaired fetal swallowing.[31,35] It is also associated with nonimmune hydrops fetalis.[36,37] The neonate has severe generalized hypotonia and weakness without myotonia, difficulties in breathing, sucking, and swallowing,[24,38,39] but there is a gradual improvement after the neonatal period. Unfortunately, children who survive are mentally retarded and later develop the underlying disease, which is gradually progressive.

Genetic counseling of affected individuals prior to pregnancy is important. The abnormal gene is localized on chromosome 19[22,40] in Type 1, and chromosome 3 in Type 2. Carrier and prenatal detection can be performed.[22,41] Subsequent generations manifest the disease more severely and at an earlier age. This phenomenon, called *anticipation*, is a unique feature of myotonic dystrophy.[42]

Myotonic dystrophy, pregnancy, and anesthesia Several cases have been described in the obstetric anesthesia literature.[43,44,45,46,47,48,49,50,51] Patients with established myotonic dystrophy may not be the ones at greatest risk, but rather those with mild disease or undiagnosed individuals.[52] Many of the latter patients may be unaware of, or fail to mention, their muscle symptoms.[53]

Respiratory and cardiac involvement should be carefully assessed since many patients have serious cardiac involvement.[54] The severity of cardiac disease does not parallel that of the skeletal-muscle disease. Most cardiac problems are due to involvement of conducting tissue.[55] Conduction abnormalities include first-degree AV block, intraventricular conduction defects, and bundle branch block. Dilated cardiomyopathy is uncommon[53,55,56] and cardiac decompensation secondary to anesthesia[57] or pregnancy occasionally occurs.[58,59] Preoperative investigations should include an EKG, even in the asymptomatic patient; Holter monitor; echocardiogram; chest x-ray; pulmonary function tests; and room-air blood gas analysis. Pulmonary function abnormalities include: reduced vital capacity, total lung capacity, and peak expiratory pressure. The diaphragm may move abnormally, and intercostal muscles are myotonic.[60] It has been suggested that a vital capacity of one liter is the minimum functional requirement necessary to maintain a successful pregnancy.[61] Invasive intraoperative monitoring depends on American Society of Anesthesiologists (ASA) physical status and the anesthetic considerations are summarized in Table 5.4. Abnormalities of the airway have been described but difficult intubation has not been reported.[50,62]

A myotonic crisis is a unique complication where the patient develops marked generalized contracture of skeletal muscles that can last 2–3 minutes. Spontaneous and controlled ventilation can be severely compromised.[7] A myotonic crisis is not relieved by neuromuscular blockade, peripheral nerve block, regional anesthesia, or general anesthesia. A generalized and/or localized contracture should be prevented by prewarming the delivery room and i.v. fluids, by the use of warming blankets, by strict avoidance of succinylcholine, by selecting an anesthetic technique that diminishes shivering, and by gentle handling of muscles during surgery (see Table 5.5). Medication for treatment should be readily available (See Table 5.6). One patient was reported to develop myotonia after propofol administration.[63] Methohexital and etomidate might be expected to produce similar responses.

Epidural anesthesia is the method of choice for labor analgesia, forceps delivery, or cesarean section (C/S). Spinal deformities are very rare in myotonic dystrophy. Spinal anesthesia may be used although it is relatively contraindicated for C/S if the respiratory system is severely compromised; combined spinal–epidural (CSE) anesthesia has been described.[64,65] Case reports suggest a reduced respiratory complication rate with regional anesthesia.[43,46,47,50]

Table 5.4 Myotonic dystrophy, pregnancy, and anesthesia: anesthetic considerations

- **Airway**
  - malocclusion
  - temporomandibular dislocation
- **Respiratory**
  - increased sensitivity to respiratory depressant drugs
  - decreased cough reflex: potential for pneumonia and atelectasis
  - postoperative respiratory failure
- **Cardiac**
  - conduction problems
  - dysrhythmia
- **Digestive**
  - aspiration
- **Obstetrical**
  - prolonged labor
  - hemorrhage
  - more frequent cesarean delivery
  - neonatal resuscitation
- **Myotonic crisis** (see Tables 5.5 and 5.6)

Table 5.5 Myotonic crisis prevention

- Warm:
  - patient
  - delivery room
  - i.v. fluids
- Avoid:
  - succinylcholine
  - shivering
- Handle muscles gently

Table 5.6 Treatment of myotonic crisis

For generalized myotonic contracture:
- procainamide (100 mg/min for a total of 1000 mg i.v. – careful, if conduction defects exist)
- dantrolene
- phenytoin

For localized myotonic contracture:
- direct injection of local anesthetic into muscle

If regional anesthesia fails, or is contraindicated for other reasons, general anesthesia can be safely administered, keeping in mind the anesthetic considerations of pregnancy and myotonic dystrophy. Respiratory-depressant drugs should be used cautiously because of diminished respiratory reserve and possible central nervous system involvement[10,60] with a preference for short-acting drugs.[66,67] Nondepolarizing neuromuscular blocking agents appear to behave normally,[68,69] but the effect of a small amount of residual muscle weakness, usually not clinically apparent in normal patients, may cause postoperative respiratory failure. Some authors[70,71] suggest that neostigmine may precipitate myotonic crisis, but others[68,72] have used it safely and report a normal response. It may be prudent to use short-acting muscle relaxants, which do not require antagonism and which have no residual effects. Malignant hyperthermia is not associated with myotonic dystrophy.[53,73,74,75,76]

The postoperative period is critical.[77,78,79] Patients should be monitored for dysrhythmias and airway obstruction, preferably in an intensive care unit setting. Physiotherapy should start as soon as possible; morbidity and mortality are usually due to respiratory problems like aspiration pneumonia or cardiac failure. Analgesia is best achieved by regional blockade and/or neuraxial opioids. Systemic opioids should be administered with caution.

Other forms of muscular dystrophy (see Table 5.7)

Other forms of muscular dystrophy are all slowly progressive diseases.[1,2,3,15,22,60,80,81,82,83,84,85,86,87,88,89] Women of childbearing age usually are not much affected. The exception is *limb-girdle muscular dystrophy* where more patients experience exacerbation of the disease in pregnancy and are at increased risk for C/S secondary to trunk-muscle weakness. There are very few case reports. As opposed to myotonic dystrophy, smooth muscle is never involved. Each parturient should be treated on an individual basis. Management should be determined after consultation with a neurologist or an internist. Pulmonary-function testing should be obtained if significant weakness is present. Antepartum ECG and echocardiography should be done. Operative delivery is more frequent. Succinylcholine should always be avoided because of the risks of hyperkalemia and rhabdomyolysis. Regional anesthesia is preferred when feasible.

Congenital myopathies (see Table 5.8)

Congenital myopathies (or sarcoplasmic myopathies) are a group of rare diseases characterized by the presence of specific abnormalities in the muscle biopsy.[1,15,88,90,91,92,93,94,95,96,97,98,99,100,101,102,103] Included in this group are: *central core*, *minicore*, *nemaline*, *distal*, and *centronuclear* myopathies. Muscle biopsy is the only way to make an accurate diagnosis since serum enzymes and electromyography (EMG) are usually normal. In most cases a pattern of inheritance has been defined. The congenital myopathies possess a number of common characteristics. Profound weakness and hypotonia are present at birth, but are usually nonprogressive. Muscle wasting and weakness are associated with secondary skeletal changes or dysmorphic features. Difficulties with tracheal intubation and regional anesthesia may occur. Succinylcholine is contraindicated *as in every primary muscle disease*. There appears to be a normal response to nondepolarizing neuromuscular blocking agents. There is a strong association between malignant hyperthermia (MH) and central core myopathy supported by clinical and laboratory evidence, including the proximity of the two genes on chromosome 19.[74,76]

King-Denborough syndrome (King syndrome) is a genetically heterogeneous phenotype that results from various congenital myopathies.[104] This syndrome is a rare disorder associated with slowly progressive myopathy, MH, kyphoscoliosis, micrognathia, malar hypoplasia, and other dysmorphic facial features similar to Noonan syndrome. These patients do not have cardiac problems, but severe respiratory compromise may be present secondary to spinal deformity and progressive myopathy. A case has been described in a woman who had an outlet forceps delivery under epidural analgesia. That patient had a tracheotomy and was ventilator dependent.[105,106]

Disorders of muscle energy metabolism (metabolic myopathies)

Fatty acids and glucose are the two most important sources of energy for skeletal muscle. Abnormalities of metabolism can be associated with rhabdomyolysis, myoglobinuria, and muscle weakness simulating muscular dystrophy.

Disorders of glycogen storage and glycolytic defects

Disorders of glycogen storage (mainly acid-maltase deficiencies) may cause muscle weakness and mimic limb-girdle muscular dystrophy or inflammatory myopathies. Reproductive potential is low, secondary to early respiratory failure or death during childhood. If patients become pregnant, demands for metabolic adjustments usually lead to fetal wastage.[1]

Disorders of glycolysis, causing exercise intolerance and myoglobinuria, can be managed with diet and prevention of stress. Two cases of successful pregnancy in glycogen storage type 1 (Von Gierke) complicated by mild preeclampsia in one, and delivered by C/S for obstetric reasons in the other, have been described.[107] Anesthesia was not described and patients had mainly metabolic imbalance controlled by different diets.

Disorders of lipid metabolism (Table 5.9)

These disorders are classified by the area of mitochondrial metabolism specifically affected.[1,22,108,109,110,111,112,113,114,115,116,117,118,119,120,121] Successful pregnancies in women with defects of substrate transport and defects of the respiratory chain have been described.[119,120,121] *Carnitine palmitoyl transferase (CPT) deficiency* is the most frequent disorder observed in this category. In these patients, it is very important to decrease stress and pain, and avoid fasting. Early neuraxial analgesia, glucose infusion, and low-outlet forceps help avoid rhabdomyolysis. Some believe that CPT deficiency and MH are related, in that both conditions can cause rhabdomyolysis.[118] In providing anesthesia to these patients, one should consider avoiding triggering drugs and

Table 5.7 Muscular dystrophy (other forms)[1,2,3,22,60,80]

Disease **Inheritance**	Onset	Clinical course	Muscular involvement	Respiratory involvement	Cardiovascular involvement	Anesthesia problems	Obstetrical problems	Specific references	Prenatal diagnosis
Facioscapulo-humeral **Dominant**	Adolescence or early adulthood.	Very slow, arrest of progression is common.	Face first, then neck, shoulder, and pelvic girdle. 10% become wheelchair-bound.	Atrophy of accessory muscles of respiration predispose to infection. Respiratory failure is rare.	Labile hypertension common. Conduction anomalies (5%), dysrhythmia, and cardiomyopathy.	Hyperkalemia with succinylcholine. Exaggerated lordosis. Postoperative respiratory problems.	–	15,81,82	Yes
Limb-girdle **Recessive** (five subtypes)	10 to 30 years old.	Progressive.	Pelvic first, then shoulder girdle.	Respiratory failure after 30 years or more of disease.	Occasional conduction anomalies, dysrhythmia, and cardiomyopathy.	Hyperkalemia with succinylcholine. Lumbar lordosis.	Wheelchair during pregnancy, prolonged second stage, increased C/S rate.	83,84,85,86,87,88	Yes
Scapuloperoneal **Dominant**	Late childhood or early adulthood.	Very slow, arrest of progession is common.	Shoulder girdle, legs, then pelvic girdle.	Uncommon.		Hyperkalemia with succinylcholine.	–	81	Yes
Congenital (includes more than one disorder) **Recessive**	Birth.	Nonprogressive, or very slowly progressive, or improve.	Generalized, proximal more than distal. Swallowing difficulties, diaphragmatic involvement.	Respiratory failure may occur much later.		Hyperkalemia with succinylcholine. Kyphoscoliosis.	–	89	

C/S = cesarean section

Table 5.8 Congenital myopathies[1,90,91]

Disease **Inheritance**	Clinical course	Muscular involvement	Respiratory involvement	Cardiovascular involvement	Anesthesia problems	Obstetrical problems	Specific references
Central core **Dominant** with variable expression	Nonprogressive.	Mild, symmetrical, proximal, face and legs.	Some	Cardiomyopathy	Airway (mandibular hypoplasia, short neck), kyphoscoliosis, **malignant hyperthermia**, lumbar lordosis.	Decreased muscle strength.	15,88,92,93,94,95,96
Minicore (Multicore) **Recessive**	Slowly progressive or nonprogressive.	Proximal, mild, trunk, face and extremities, swallowing difficulties.	Recurrent chest infections secondary to kyphoscoliosis, diaphragmatic weakness and chronic aspiration. Nocturnal hypoventilation.	Cardiomyopathy (rare).	Kyphoscoliosis		97
Nemaline (rod body) Four forms, most common form is **Recessive**	Slowly progressive or nonprogressive.	Mild, generalized, symmetrical, proximal, swallowing difficulties.	Chronic aspiration, microatelectasis secondary to diaphragmatic involvement. Nocturnal hypoventilation.	Cardiomyopathy, congenital heart disease (rare).	Airway (high-arched palate, micrognathia), kyphoscoliosis, lumbar lordosis, and other dysmorphic features, aspiration.	Dystocia	98,99,100,101,102
Centronuclear (myotubular) **Dominant or sex-linked**	May or may not be progressive.	Generalized		Cardiomyopathy (rare).	Airway (high-arched palate), kyphoscoliosis.		103

Table 5.9 Disorders of muscle energy metabolism [1,22,108,109,110]

Disease **Inheritance**	Onset	Clinical course	Muscular involvement	Respiratory involvement	Cardiovascular involvement	Anesthesia problems	Obstetrical problems	Specific references
Carnitine deficiency, systemic form **Recessive**	Childhood	Progressive weakness, death secondary to irreversible coma. Treatment: carnitine supplement and carbohydrate.	Proximal, improved with carnitine supplement in some cases.	Possible	Rare cardiomyopathy.	Avoid fasting, sux, shivering, hypoglycemia, metabolic acidosis. Recurrent hepatic encephalopathy.	Postpartum rapid progression of weakness if no treatment, death.	111,112,113,114
Carnitine deficiency, myopathic form **Recessive**	Childhood	Slowly progressive. Treatment: carnitine supplement and diet.	Proximal, can affect pharyngeal muscles.	Progress to respiratory failure.	Cardiomyopathy	Rhabdomyolysis	–	115
Carnitine-palmitoyl-transferase deficiency **Recessive**	Childhood	Normal strength between attacks. Treatment: high carbohydrate and low fat diet.	Weakness is induced by fasting and exercise, and may be severe and generalized. Muscle cramps.	May require respiratory assistance during episode of weakness.		Rhabdomyolysis precipitated by fasting, exercise, sux, NSAID. Avoid shivering, give glucose.	Rhabdomyolysis in labor, normal uterine muscle tone despite abnormal muscle biopsy.	116,117,118,119,120,121
Complex III deficiency	Childhood	Slowly progressive.	Mild generalized weakness, muscle cramps, exercise intolerance.	Decreased O_2 consumption, increased CO_2 production.	WPW in one case report.	Severe lactic acidosis, prevent shivering.	Preterm labor, avoid labor, elective cesarean section.	

sux = succinylcholine; NSAID = nonsteroidal anti-inflammatory drug; WPW = Wolff-Parkinson-White

ensure temperature monitoring. In addition, propofol may be contraindicated because of the propofol infusion syndrome (PRIS). Propofol infusion syndrome, manifested by life-threatening myocardial failure and metabolic acidosis, was reported first in a pediatric intensive care unit patient, but more recently in patients affected with disorders of lipid metabolism. The long-chain triglycerides present in the lipid vehicle of propofol may play a role in the development of PRIS.[122,123]

Mitochondrial myopathy

Mitochondrial myopathies are rare diseases caused by genetic defects in the morphology of mitochondria. A maternal mode of inheritance is characteristic of many mitochondrial diseases, because mitochondrial DNA is transmitted by the oocyte. Some forms are very severe and patients are extremely handicapped. Mitochondrial myopathy is characterized by fixed proximal weakness with marked exercise intolerance. Rhabdomyolysis is rare. Skeletal-muscle biopsy is characteristic (ragged red fibers). Reports of pregnancies with normal progression of labor, epidural analgesia, and assisted delivery have been described.[124,125,126] Epidural analgesia prevents lactic acidosis during labor and enables the use of outlet forceps or vacuum for delivery.

Disorders of muscle membrane excitability

These diseases are characterized by myotonia and, as opposed to myotonic dystrophy, they do not present with significant permanent muscle weakness until late in their course. Myotonia is a persistent contraction of a muscle observed after cessation of voluntary contraction.[127] These disorders are amenable to treatment, and with effective preventative measures progressive weakness can be avoided. Diagnosis is based on clinical history and confirmed by measuring serum electrolytes during attacks, by provocative tests or by DNA analysis. Although it is difficult to interpret caffeine-halothane contracture tests in myotonic patients, most authors believe that they are not MH susceptible.[128,129,130,131,132,133] Clinical features, prevention, treatment, anesthetic, and obstetrical problems are summarized in Table 5.10.[134,135,136,137,138,139,140,141,142,143,144,145]

Calcium channel disorders of muscle (hypokalemic periodic paralysis)

Previously known as dyskalemic periodic paralysis, *hypokalemic periodic paralysis* is now classified as a calcium channel disorder of muscle.

Chloride channel disorders of muscle (= myotonia congenita = Thomsen disease)

Myotonia congenita is a rare inherited autosomal-dominant disease. Symptoms may be present from birth, but usually appear later. This mild, nonprogressive disease is characterized by generalized, cold-aggravated, painless myotonia, and muscular hypertrophy. Males are more severely affected than females. The main complaint is one of stiffness and the affected individual may not be aware of the diagnosis.[146] Stiffness on initiating voluntary movement is relieved by exercise ("warm-up" phenomenon). There is no muscular weakness or involvement of other organs. Smooth muscle is never affected, thus uterine contractions are normal. Temporary worsening of myotonia can occur in the second half of pregnancy.[147] Treatment is with an oral lidocaine-like antidysrhythmic agent. Therapy is used frequently because the myotonia is more incapacitating and drug use is safer in these patients. This is in contrast to myotonic dystrophy where cardiac involvement limits drug therapy. Several variants of this condition have been described,[148] including the more severe autosomal-recessive form (Becker myotonia).

Epidural, spinal, or general anesthesia can be used safely as long as precipitation of a myotonic crisis is prevented as described previously (see Table 5.5) and treatment is readily available (see Table 5.6) Response to nondepolarizing muscle relaxants is normal.[68]

Sodium channel disorders of muscle (hyperkalemic periodic paralysis, paramyotonia congenita, and potassium aggravated myotonia = sodium channel myotonia)

Paramyotonia congenita is the rarest of the myotonic syndromes. It is transmitted as an autosomal-dominant characteristic. The myotonia is termed paradoxical because the muscular stiffness is exacerbated by exercise.[127] Paramyotonia congenita is a nonprogressive illness and, for most patients, the symptoms are more of a nuisance than a handicap. As in myotonia congenita, there is a tendency to muscle hypertrophy. It affects mostly the face, tongue, neck, and hand muscles, and occasionally leg muscles. Paramyotonia congenita is commonly induced or aggravated by exposure to cold, or after exercise. Usually, symptoms respond rapidly to warming but episodes of flaccid paralysis lasting several hours after the muscles have rewarmed may occur. Pretreatment with tocainide prevents or improves the symptoms in all patients.[149] There appears to be no other organ system involved. Doubt has arisen as to whether paramyotonia congenita and hyperkalemic periodic paralysis are separate entities.[127,150] There is increasing evidence to suggest that they are allelic disorders, the locus having been traced to chromosome 17.[151] The predominant feature of paramyotonia congenita is *myotonia*, whereas in hyperkalemic periodic paralysis the main clinical symptom is *muscle weakness*.[134] In severely affected women, symptoms may be worse during pregnancy.[134,149] A case report suggested that a cold-induced abdominal wall contraction led to premature labor and delivery.[152] Subsequently, the same patient had another pregnancy with a normal delivery and an epidural without any problem.[153] Anesthetic considerations are the same as for myotonia congenita (see Table 5.10).[154]

Inflammatory myopathies

Inflammatory myopathies have an autoimmune origin and can be classified into three groups: *dermatomyositis* (DM),

Table 5.10 Disorders of muscle membrane excitability[134,135]

Disease **Inheritance**	Onset	Muscular involvement	Provocation of attacks	Duration of attacks	Respiratory involvement	Cardiac involvement	Treatment	Anesthesia problems	Obstetrical problems	Case reports	Prenatal diagnosis
Hypokalemic **Dominant calcium channel disorder**	Late first or second decade. Male more severely affected.	Proximal limbs progressing to trunk and neck, rarely bulbar or respiratory muscles.	Rest after exercise, high sodium or carbohydrate meal, bicarbonate, glucose, insulin, adrenalin, corticosteroid, cold, stress, infection, trauma, menstruation.	2 to 4 hours to days.	Rarely respiratory distress can be fatal.	Fluid retention, bradycardia, dysrhythmia, cardiac failure.	Acute: KCL; Prevention: acetazolamide + KCL, early epidural analgesia for vaginal delivery with a passive second stage.	Avoid: hypokalemia, sux, glucose load, alkalosis. monitor EKG, K^+ and glucose. Keep warm. NDMR safe.	PIH. More frequent and worse crises.	136,137,138,139 140,141,142	
Hyperkalemic **Dominant sodium channel disorder**	Infancy and childhood.	Proximal limbs progressing to trunk and face.	Fasting, cold, rest after exercise, KCL, corticosteroid.	2 to 3 hours.	Mild weakness.	Dysrhythmia.	Acute: glucose and insulin or calcium gluconate; Prevention: acetazolamide, frequent meals.	Avoid: fasting, sux, KCL. Monitor EKG, K^+, glucose. Give glucose. Keep warm. NDMR safe.	PIH. More frequent and worse crises.	143,144,145	Possible

KCl = potassium chloride; sux = succinylcholine; EKG = electrocardiogram; NDMR = nondepolarizing muscle relaxant; PIH = pregnancy-induced hypertension

polymyositis (PM) and *inclusion-body myositis*. Classic diagnostic criteria are: proximal muscle weakness, elevated muscle enzymes (50-fold above normal), abnormal EMG findings, muscle biopsy and, more recently, autoantibody profile, and magnetic resonance imaging.[155] Myoglobinuria is rarely observed.[156] Steroids are considered the mainstay of treatment in most cases. Treatment should be continued during pregnancy in accordance with disease activity. Immunosuppressive therapy should not be used unless the mother's life is at risk. Patients with DM have skin involvement early in the onset of the disease, but skin changes may precede or follow muscle involvement. The typical rash and myositis allow a diagnosis of DM. A flare is an exacerbation or crisis and is usually less of a problem for patients with DM. The skin changes include various eruptions, erythema, and dermatitis. The classic lilac-colored (heliotrope) rash occurs on eyelids, bridge of nose, and cheeks (butterfly distribution). Affected women respond well to therapy and generally recover their muscle strength completely after each relapse. Polymyositis is more prone to flares without complete recovery of muscle strength. Inclusion-body myositis responds poorly to treatment and is the most frequent form of inflammatory myositis in patients over 55 years of age, mainly in men.

Extramuscular manifestations may be present to a varying degree. Heart involvement is always present with EKG abnormalities (atrial dysrhythmias or conduction abnormalities) and elevated cardiac enzymes, and may lead to congestive heart failure. Severe dysphagia requires aggressive treatment due to the risk of pulmonary aspiration. Cricopharyngeal myomectomy may be required. Neck flexors may be affected. Interstitial lung disease may be rapidly progressive in up to 10% of patients. Weakness of the intercostal muscles and diaphragm can contribute to ventilatory insufficiency. Malignancies are increased in patients with DM. The *overlap syndrome* describes the association of an inflammatory myopathy and a connective-tissue disease (such as scleroderma, rheumatoid arthritis, or systemic lupus erythematosis). The best described association is DM with systemic sclerosis,[157] which is associated with poor recovery of function.

Since the peak incidence of DM occurs between 40 and 60 years of age, there are only a few reported cases associated with pregnancy. Even in patients with controlled disease, fetal outcome may be adversely affected,[156] but many healthy infants have been born to mothers with DM.[158,159,160,161] Dermatomyositis and polymyositis may be triggered by pregnancy, but only a small proportion of patients with the disease show clinical exacerbation during pregnancy. Pregnancy-induced hypertension and placental abruption have been described with other connective-tissue diseases, but not in DM or PM patients.

Monitoring muscle strength during pregnancy is the best way to assess disease activity. Multidisciplinary consultations should be obtained, especially to evaluate respiratory muscle involvement, dysphagia, and cardiac abnormalities. Uterine muscle is unaffected. Extreme weakness could necessitate assisted labor and delivery, but is not reported.

Anesthetic management for pregnant patients with DM or PM has not been described. Regional anesthesia seems appropriate for labor, especially if muscular weakness is important, and could be of use if a C/S is needed.

General anesthesia has been described in patients with DM or PM.[162,163] Succinylcholine should not be used for rapid sequence induction, especially in patients with significant muscle necrosis.[60] Dermatomyositis and polymyositis are rare diseases and severe hyperkalemia, myoglobinuria, and MH have not been described.[7] Responses to nondepolarizing muscle relaxants seem to be normal.[162] Any residual drug effect for neuromuscular blockade or analgesia may lead to ventilatory insufficiency and pulmonary aspiration in severely affected women.

Tumors and masses

Myositis ossificans progressiva

Myositis ossificans progressiva is a rare, autosomal-dominant disease characterized by extraskeletal ossification involving muscle connective tissue.[164] The disease usually starts in early childhood and is progressively debilitating. Patients develop diffuse lesions that may be exacerbated by attempts at excision. Disodium ethane 1-hydroxy-1,1- disphosphate (EHDP) halts the progression of the disease, but well-formed ossifications do not regress.[165] As the disease progresses, patients develop severe limitation in chest motion with the potential for secondary respiratory and cardiac failure.[80] Fertility is reduced and early pregnancy loss is common. The first reported case of pregnancy associated with myositis ossificans progressiva was an induced abortion at ten weeks' gestation.[164] The only case report of a successful pregnancy described a C/S performed under local anesthesia and sedation for a 26-week viable infant.[166] Intubation of these patients may be impossible, even with the use of a fiberoptic bronchoscope, because of a fixed and flexed position of the neck. Tracheostomy may be difficult because of extensive calcification of the tracheal rings. Regional anesthesia depends on the extent of existing kyphoscoliosis. Anesthetic and obstetrical considerations are summarized in Table 5.11.

Table 5.11 Myositis ossificans progressiva

Anesthetic Considerations

- **Airway**:
  - difficult intubation (fixed neck and jaw)
  - calcification of tracheal rings preventing rapid tracheotomy
- **Musculoskeletal**:
  - kyphoscoliosis
- **Respiratory**:
  - restrictive syndrome secondary to a fixed ribcage
- **Obstetrical**:
  - fixed hip joints
  - cesarean delivery
  - tissue calcification in the wound

Summary

Myopathies are diseases of the skeletal muscle cell with intact innervation. Pregnant women with myopathies have specific needs depending on the symptoms and severity of their disease. The potential for anesthetic agents or techniques to induce MH, hyperkalemia, or myotonic crisis must be assessed in the antenatal period. Multidisciplinary consultation early in the pregnancy is, therefore, the key to a successful outcome.

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6 PARTURIENTS OF SHORT STATURE

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Introduction

Dwarfism is defined as failure to achieve a height of 4 feet 10 inches (148 cm) at adulthood.[1] Short stature is a clinical entity that has numerous etiologies. These conditions can be of genetic, constitutional, or metabolic origin. There are more than 100 different types of dwarfism, none of which is very common. The most common variety, achondroplasia, occurs in only 0.5 to 1.5 per 10 000 live births.[2,3] Two major classifications of dwarfism are especially useful to the anesthesiologist: (1) patients with short stature who are *proportionate* and have normal trunk-to-limb ratio, and (2) patients who have *disproportionate* growth and have either short trunks in relation to their limbs or short limbs in relation to their trunks. (see Table 6.1).[2] There are women at the lower extreme of height in some cultures who would meet the definition of dwarfism but who have no medical pathology. Their treatment must be individualized bearing in mind that they may be similar in some respects to parturients with proportionate dwarfism.

Since the formation of the Little People of America, a society for people of short stature, and even dedicated online dating services, much greater opportunity exists for dwarfs to meet, socialize, and eventually have children. In addition, increased use of assisted reproductive technology is enabling women of short stature who were otherwise infertile to achieve pregnancy and even multiple gestations. As a result, it is likely that more pregnant dwarfs will present for medical care in the future, often with comorbidities, high-risk multiple gestation pregnancies,[4,5] and frequent need for cesarean delivery.

Proportionate short stature

This category of dwarfism refers to those people who have short stature with proportionate trunk-to-limb length ratio. Individuals may have proportionate short stature as a result of an endocrine deficiency, metabolic disorder, or long-standing cardiac, renal, neurologic, or gastrointestinal disease.[6] Although some of these patients are infertile or do not survive long enough to reach childbearing age,[6] those with an endocrinological etiology are frequently capable of becoming pregnant. Two endocrine disorders, which cause proportionate short stature and may be seen in pregnancy, are *isolated growth hormone deficiency* and *Laron dwarfism*.

Isolated growth hormone deficiency

Four types of this condition exist. These patients vary in terms of mode of inheritance (autosomal dominant, autosomal recessive, X-linked) as well as in their degree of hormonal deficiency.[7] It is possible for other hormonal deficiencies to be present in conjunction with human growth hormone (hGH) deficiency (e.g. decreased levels of luteinizing hormone [LH], follicle stimulating hormone [FSH], thyroid stimulating hormone [TSH], and adrenocorticotropin hormone [ACTH] in panhypopituitary patients), in which case puberty may not occur, making pregnancy unlikely in these individuals.[7] The other tropic hormones appear to be normal in pregnant hGH-deficient patients.[8]

A common type of isolated growth hormone (GH) deficiency is seen in ateliotic dwarfs, who carry an autosomal recessive gene. This gene causes a decrease in hGH production.[9] Ateliotic dwarfs are typically of normal weight and length at birth, but over the next few months of life have a much slower growth rate than unaffected infants. Their height rarely exceeds 130 cm, the height of a normal eight-and-a-half year old.[1] Those who achieve sexual maturation, known as sexual ateliotics, may not reach puberty until the late second or third decade of life. In addition to having short stature, these individuals have soft, prematurely wrinkled skin, high-pitched voices, and may have mild micrognathia. Some patients also lack a normal lumbar lordosis.[1,8]

Isolated GH deficiency is not usually diagnosed by random blood samples of hGH alone, because these levels are normally low throughout most of the day. Provocative tests are more frequently used, including measurement of hGH after stimulation by exercise, L-dopa, insulin, arginine, clonidine, glucagon, or a combination of these.[7] Some GH-deficient dwarfs have abnormal glucose metabolism or responses to insulin, with glycosuria in early gestation progressing later to gestational diabetes.[1] These patients should be thoroughly investigated in the antenatal period to detect and control any glucose perturbations during pregnancy.

Laron dwarfism

This is an autosomal recessive disorder, which is clinically very similar to isolated GH deficiency. However, Laron dwarfs have increased release but resistance to GH, very low serum levels of insulin-like growth factor (IGF-I), and an abnormal GH receptor.[10] In addition to having a normally proportioned trunk and extremities, these individuals may have frontal bossing, saddle nose, acromicria (hypoplasia of the extremities of the skeleton – the nose, jaws, fingers, and toes),[11] a high-pitched voice, and slow and sparse hair growth.[12]

Effects of pregnancy

The normal physiologic changes of pregnancy can have serious implications for maternal health in proportionate dwarfs with the

Obstetric Anesthesia and Uncommon Disorders, eds. David R. Gambling, M. Joanne Douglas and Robert S. F. McKay. Published by Cambridge University Press.

Table 6.1 Classification of dwarfism

I. Proportionate short stature
  A. Endocrine etiology
    1. Isolated growth hormone deficiency
    2. Laron dwarfism
  B. Constitutional
  C. Chronic disease states
II. Disproportionate short stature
  A. Osteochondrodysplasias – abnormalities of cartilage +/− bone growth and development
    1. Achondroplasia
    2. Pseudoachondroplasia
    3. Spondyloepiphyseal dysplasia congenita
    4. Spondyloepiphyseal dysplasia tarda
    5. Spondylometaphyseal dysplasia
    6. Diastrophic dwarfism
    7. Osteogenesis imperfecta
  B. Primary metabolic abnormalities
    1. Calcium derangements
    2. Phosphorous derangements
    3. Complex carbohydrate derangements

Table 6.2 Vertical and horizontal abdominal measurements in nonpregnant individuals (cm)

	Achondroplasia	Ateliotic	SED & Diastrophic	Normal
Xiphoid to Symphysis	29	25	24	33
Intercristal	21	24	25	30

SED = Spondyloepiphyseal dysplasia
Reprinted with permission from Tyson, J. E., Barnes, A. C., McKusick, V. A. *et al*. Obstetric and gynecologic considerations of dwarfism. *Am. J. Obstet. Gynecol*. 1970; **108**: 688–703.

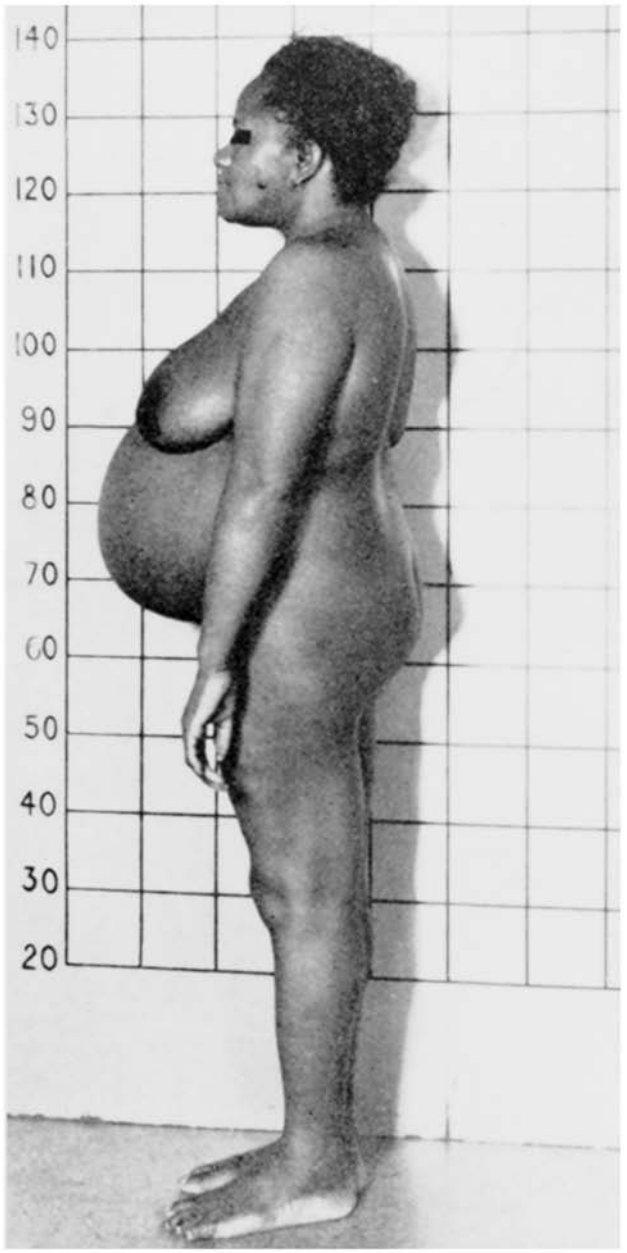

Figure 6.1 Patient L. L. An ateliotic dwarf in the 28th week of gestation. Reprinted with permission from C. V. Mosby Co. from Tyson, J. E., Barnes, A. C., McKusick, V. A. *et al*. Obstetric and gynecologic considerations of dwarfism. *Am. J. Obstet. Gynecol*. 1970; **108**: 688–703.

most concerning cardiorespiratory embarrassment. The abdominal dimensions of these patients are markedly smaller than their normal-sized counterparts. For example, the average distance in nongravid individuals from xiphoid to symphysis is significantly less in ateliotic dwarfs than in normal-sized patients (see Table 6.2). The uterus therefore becomes an intra-abdominal organ earlier in gestation (see Figure 6.1). These factors may cause significant mechanical diaphragmatic dysfunction and greater aortocaval compression. The decrease in functional residual capacity (FRC) that normally occurs during pregnancy causes additional respiratory compromise.[13] Pregnant dwarfs may suffer from decreased vital capacity, hypoxia, and acidosis, and develop tachypnea and tachycardia in order to compensate for these physiologic derangements. Deterioration of pulmonary status may warrant immediate delivery of the fetus in order to improve maternal condition.[1]

Obstetric management

Some authors believe that almost all pregnant patients of short stature should be delivered by cesarean section (C/S).[14] Others report ateliotic patients who have had successful vaginal deliveries but no details are available.[1] The pelvic diameters of such patients are typically smaller than those of parturients of normal stature and are frequently only sufficient for delivery of a premature infant.[1] Cesarean section is thus performed frequently for

cephalopelvic disproportion as well as to relieve maternal cardiopulmonary embarrassment.

Other complications of pregnancy include higher than normal rates of spontaneous abortion, stillbirth, and premature delivery.[1] It is unclear whether these complications result from a mechanical, genetic, or hormonal problem; however, premature delivery is more likely when maternal respiratory embarrassment is present.[1] It has been suggested that preterm delivery[16] may be due to some unknown physiological actions of GH in the first half of pregnancy, prior to placental production of a variant type of GH.[15] Additionally, there is a higher incidence of premature birth secondary to maternal indications.[1]

Anesthetic considerations (see Table 6.3)

One case report describes a patient with pituitary dwarfism who was 124 cm tall and weighed 35 kg at 36 weeks' gestation.[16] Because of anticipated fetal weight of almost 3000 g at that time, she had a planned C/S under epidural anesthesia at 39 weeks' gestation. The epidural catheter was placed easily and she received 12 ml of 2% lidocaine with 1:200 000 epinephrine and 50 μg of fentanyl to achieve a T3 sensory level. Her perioperative course was uneventful and she received 2 mg epidural morphine for postoperative analgesia.[16]

Preoperative consultation should include a history and physical examination with emphasis on the airway and anatomical landmarks relevant to regional anesthesia. If respiratory compromise is present, arterial blood gas analysis, pulmonary function tests, and chest radiographs may be indicated. Measurement of oxyhemoglobin saturation using pulse oximetry with the patient in the upright and Trendelenburg positions is a useful screening test to detect potential deterioration with decreases in FRC. No additional laboratory or radiological studies are necessary in the absence of other complicating conditions. Routine noninvasive monitoring is adequate during labor and delivery in patients without other complicating factors. If respiratory problems are present, intra-arterial catheter placement with monitoring of oxygenation, ventilation and acid-base status may be prudent.

In those instances where vaginal delivery is anticipated, intravenous (i.v.) or intramuscular opioids may be useful. However, epidural analgesia provides superior pain relief without respiratory depression and is the technique of choice. The appropriate dose of a dilute local anesthetic, in combination with an opioid, can be titrated slowly in order to achieve adequate analgesia. Patient-controlled epidural analgesia can be used for maintenance with conservative bolus doses, approximately half to two-thirds of the initial bolus volume, used initially. If C/S is necessary, as is frequently the case, additional local anesthetic can be injected to provide surgical anesthesia. Careful titration is essential to avoid high epidural blockade with the potential for respiratory embarrassment.

For patients undergoing planned C/S, a continuous technique is preferable to a single-shot technique. We prefer continuous epidural over continuous spinal anesthesia because of the lower incidence of headache and perhaps lower potential for neurologic deficit. However, a continuous spinal anesthetic can be used with slow titration of local anesthetic to provide adequate neural blockade. Although recent radiologic evidence suggests that adult patients with Laron syndrome have narrowing of the spinal canal at the cervical level, little is known about stenosis of the lumbar region.[17] It is presumed that the spinal cord is proportionately reduced in size relative to the volume of the spinal canal, but this is not known for certain. If the spinal cord were to be large in relation to the size of the spinal canal, or to terminate at a lower than expected level, an increased risk of neurologic damage with regional (particularly spinal) anesthesia might be present. However, in an emergency situation, a continuous spinal might provide more rapid onset of anesthesia than an epidural.

As in individuals of normal size, a test dose can be used to identify inadvertent epidural catheter placement in the subarachnoid space or in an epidural vein. Test doses for labor analgesia are controversial but we believe that a test dose is useful when surgical analgesia is desired. The optimal test dose in dwarfs is unknown, but it is prudent to reduce the dose of local anesthetic and consider the dose of epinephrine on the basis of patient weight. In the case mentioned above, a 2 ml test dose of 2% lidocaine with 1:200 000 epinephrine was used safely.[16] It was felt that, in the event of an inadvertent subarachnoid injection, this dose would have provided evidence of spinal blockade without producing an excessively high level. The dose of 10 μg of epinephrine may have been inadequate for identification of intravenous placement of an epidural catheter, compared with the more commonly accepted 15 μg dose.[18] However, on a microgram per kilogram basis, the epinephrine dose was slightly greater than that normally used. Careful incremental injection of local anesthetic is critical to avoid risk of i.v. injection or high segmental block.

Although a single-dose spinal anesthetic can be performed, the appropriate dosage of local anesthetic may be difficult to predict because of the presence of a shortened spinal cord. Local

Table 6.3 Anesthetic considerations for proportionate dwarfs

Dwarfism characteristics	Anesthetic implications
Upper airway	
Micrognathia possible	Possible difficult intubation
Smaller airway	May need smaller ETT
Cervical spine	High incidence of spinal stenosis
	Possible atlantoaxial instability
Short stature	Decreased dosage of local anesthetic for regional anesthesia
	Continuous regional technique is preferred
Small pelvis	High rate of cesarean section
Uterine impingement on intrathoracic structures	Respiratory compromise
	May not tolerate supine position or rapid i.v. fluid administration
Uterine impingement on abdominal structures	Risk of supine hypotension
	Risk of aspiration

anesthetic doses comparable to those used in the pediatric population may be appropriate. However, no studies have been performed in this population to confirm this. Potential problems with subarachnoid blockade include underdosage, resulting in inadequate anesthesia for C/S, as well as overdosage, resulting in high spinal anesthesia with the risk of loss of airway control, respiratory arrest, hemodynamic instability, and cardiac arrest.

While some authors have advocated general anesthesia (GA) for all patients with nonproportionate short stature,[14] no such recommendation exists for dwarfs with proportionate short stature. However, since descriptions of such dwarfs have included micrognathia as a clinical feature, difficult intubation is a potential problem. Furthermore, a prospective study performed on patients with Laron syndrome found a high incidence of cervical spinal stenosis, atlanto-odontoid osteoarthritic changes, and a decreased mediolateral diameter of the oropharynx. These findings led the authors to recommend routine cervical spine imaging (preferably magnetic resonance imaging [MRI]) in these patients. We believe MRI should be performed if time permits.[17] Regardless, caution should be used and a thorough airway evaluation performed prior to induction of GA in order to avoid difficulties with airway management. If imaging of the cervical spine is not available, awake fiberoptic intubation should be considered, especially in patients with symptoms consistent with cervical spinal column narrowing.

Prediction of the appropriate size of endotracheal tube (ETT) for proportionate dwarfs is difficult. Whereas age is usually the best guide to ETT size in children, weight was found to be a better predictor in pediatric patients with proportionate small stature.[19] Precautions against aspiration are particularly important in pregnant dwarfs because the uterus causes additional impingement on intra-abdominal structures.[20,21] For the same reason, supine hypotension may be more problematic than in the normal-size parturient.

Pain management after C/S can utilize epidural opioids, preferably in a reduced dosage, but no schedule for appropriate dosage of epidural opioids exists in dwarfs. In view of the potential risk for respiratory depression, we recommend a high level of postoperative monitoring including frequent vital signs and use of continuous pulse oximetry for 16–24 hours.

Neonatal considerations

Infants born to mothers with isolated GH deficiency are usually of normal birth weight and length.[8] The diagnosis of dwarfism in the offspring is made either in infancy or in childhood, as growth does not progress at a normal rate. Laron dwarfs have birth lengths that are abnormally shorter than average, with a normal birth weight.[7] Considerations for immediate neonatal resuscitation are similar to those for other infants born to mothers with a small pelvis.

Disproportionate short stature

Patients with disproportionate short stature are potentially more complicated from an anesthetic perspective than those with proportionate short stature. Etiologies of disproportionate short stature include the osteochondrodysplasias (abnormalities of cartilage and/or bone growth and development) and primary metabolic diseases that involve the skeleton.[2,22] Patients with primary metabolic diseases frequently do not survive into adulthood or are infertile.

Achondroplastic dwarfism

Achondroplastic dwarfism is the most common type of dwarfism, with a prevalence rate of 0.5 to 1.5 per 10 000 births.[3] A summary of the anatomic and physical characteristics of achondroplasia is listed in Table 6.4. Short stature in this condition is a result of abnormal endochondral bone formation. These patients have normal truncal lengths, but shortened limbs, which are primarily responsible for their short stature. Achondroplastic dwarfs are usually no taller than 130 cm.[2] The disease is caused by a mutation in the fibroblast growth factor receptor gene, which results in decreased endochondral ossification.[23] The mode of inheritance

Table 6.4 Achondroplasia: anatomic and physical findings

General:	Normal trunk length
	Short limbs
Craniofacial:	Megalocephaly – large head size
	Megalencephaly – large brain size
	Brachycephaly – short head
	Foramen magnum stenosis
	Decreased atlanto-occipital distance
	Frontal bossing
	Depressed nasal bridge
	Maxillary/facial hypoplasia
	Macroglossia
	Narrowed upper airways
Central nervous system:	Hydrocephalus
	Hypotonia
Spine/skeletal:	Generalized spinal stenosis
	Odontoid dysplasia
	Atlanto-axial instability
	Abnormally shaped vertebrae
	Hyperplastic intervertebral discs
	Lumbar hyperlordosis
	Thoracolumbar kyphosis
	Square ilia
	Narrow sciatic notch
	Horizontal sacrum
Respiratory/cardiac:	Chest deformities
	Thoracic dystrophy/kyphosis
	Rib hypoplasia
	Upper airway obstruction
	Obstructive sleep apnea
	Cor pulmonale
	Possible pulmonary hypertension

in achondroplasia is autosomal dominant, although 80% are a result of spontaneous mutation.[23,24]

Achondroplastic dwarfs usually are diagnosed at birth, and have numerous craniofacial abnormalities such as megalocephaly (large head size), megalencephaly (overgrowth of the brain), frontal bossing, and a depressed nasal bridge (see Figure 6.2).[2,11] Maxillary hypoplasia, a large mandible, and a large tongue may be present in these individuals,[25] and indicate a potential for difficult airway management. In a series of 36 anesthetics performed in 27 patients, Mayhew *et al.*[25] reported no difficulty in airway management either with mask ventilation or direct laryngoscopy. In a report by Monedero *et al.*[26] airway complications did not occur during 53 general anesthetics for 15 mostly pediatric achondroplastic patients undergoing orthopedic surgery. However, the report described one patient in whom it was impossible to visualize the larynx, so intubation attempts were abandoned and a laryngeal mask airway (LMA) was placed. The same patient required endotracheal intubation with the aid of a stylet on another occasion. One case report of difficult intubation in achondroplastic patients attributes the problem to limited neck extension[27] while another describes difficulties due to subglottic stenosis.[28]

Numerous spinal anomalies can occur in achondroplastic dwarfs. Thoracolumbar stenosis and generalized spinal stenosis are frequent findings.[29,30,31,32] Additional abnormalities include lumbar hyperlordosis and/or thoracolumbar kyphosis, thoracic dystrophy, square ilia, a narrow sciatic notch, and a horizontal sacrum. Because of the lumbar lordosis, the fifth lumbar vertebra seems to have a lower position relative to the ilia than is seen in the nondwarf population.[33]

Narrowing of the spinal canal (spinal stenosis) can occur at any spinal level,[33] although the thoracolumbar and lumbar regions

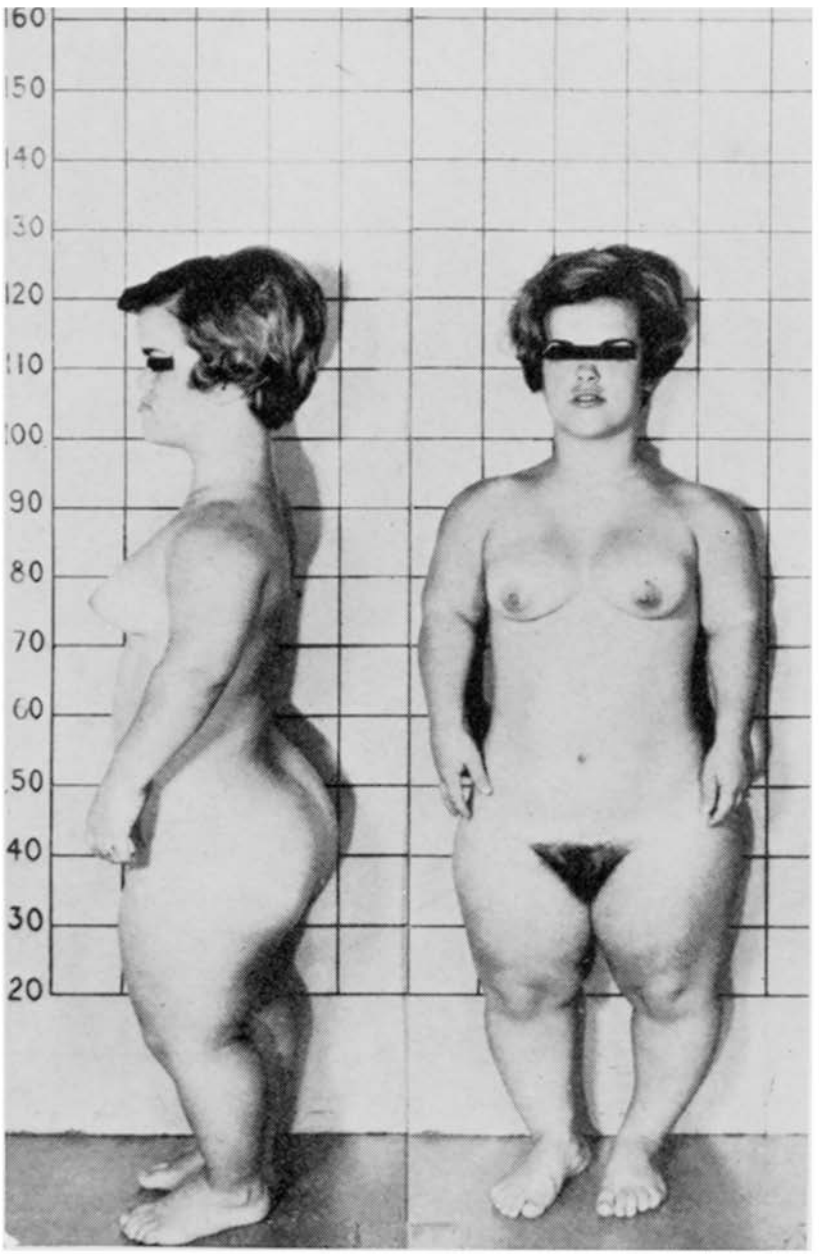

Figure 6.2 Achondroplasia associated with short limbs, characteristic facies, and contracted pelvis. Reprinted with permission from C. V. Mosby Co. from Tyson, J. E., Barnes, A. C., McKusick V. A. *et al*. Obstetric and gynecologic considerations of dwarfism. *Am. J. Obstet. Gynecol*. 1970; **108**: 688–703.

are the most commonly narrowed segments in achondroplastic dwarfs. Spinal cord compression can result from narrowing due to abnormally shaped vertebrae or hyperplastic intervertebral discs.[29] The narrowing of the spinal canal from underdeveloped vertebral arches and shallow vertebral bodies results in a narrowed epidural and subarachnoid space,[34] which has anesthetic implications when regional anesthesia is attempted.

Additionally, the abnormal intervertebral discs frequently bulge laterally and posteriorly and can cause neurologic deficits.[2,35] Anatomic findings in one cadaveric achondroplastic spine from a patient who had suffered from nonvascular claudication symptoms revealed thickened pedicles, inferior facet encroachment, and nerve root stenosis.[36] These physical findings were consistent with the symptomatology seen in this patient prior to death from an unrelated cause. Because symptoms of neurologic compromise can progress to paralysis,[29,32,33,36,37,38,39,40] it is critical for the anesthesiologist to be aware of and document any neurologic symptoms prior to anesthetic intervention. In a series of 46 pregnant dwarfs, 4 out of 26 achondroplastic patients had symptoms of nerve root compression consisting of numbness and tingling in the lower limbs.[14] No mention is made of the route of delivery, use of forceps, size of the infant, use of regional anesthesia, duration of pushing while in stirrups, or other details of the obstetric course of these patients.

While there are no studies to define the safety of regional anesthesia in achondroplastic patients with spinal stenosis, the implications of regional anesthesia in patients (not of short stature) with spinal stenosis are outlined by Moen *et al.*[41] In this study, the incidence of paraparesis or cauda equina syndrome following neuraxial anesthesia was approximately 1:400 000 and 1:50 000 respectively. However, all patients with paraparesis and almost one-third of patients with cauda equina syndrome were subsequently found to have spinal stenosis. A full neurological exam and possibly imaging studies are recommended for achondroplastic patients. If the patient has neurologic deficits, neurogenic claudication, and/or has spinal stenosis without symptoms, she should be advised of the rare but increased risk of neurologic injury associated with regional anesthesia. If she has severe spinal stenosis, it may be advisable to avoid regional anesthesia, just as in individuals of normal stature.

Foramen magnum stenosis due to bony hypertrophy is also a common finding in achondroplasia[2] and can result in medullary and upper-cervical neurologic deficits. Care must be taken to limit hyperextension of the head in order to avoid exacerbating previous deficits and causing new cervical spinal cord injury.[30,42,43,44,45] It is important for the anesthesiologist to question the patient regarding neurologic symptoms prior to institution of GA or performance of direct laryngoscopy and intubation.

Hypotonia and hydrocephalus are also features seen in achondroplasia, although hydrocephalus does not always require ventricular shunting.[2,33] Progressive hydrocephalus with concomitant elevations in intracranial pressure (ICP) may warrant shunting. The mechanism for hydrocephalus in these dwarfs is thought to be intracranial venous hypertension or cerebrospinal fluid (CSF) flow obstruction at the level of the stenosed foramen magnum.[46,47,48]

In addition to the neurologic problems described above, respiratory complications occur commonly. In one survey,[14] 4 out of 26 achondroplastic pregnant women had respiratory difficulties during the last two months of gestation. The etiologies include chest deformities, upper airway obstruction, sleep apnea, neurologic problems, and other unrelated pulmonary conditions.[3] Thoracic cage deformities, including rib hypoplasia and other rib deformities, can cause restrictive lung disease. Additionally, these mechanical problems may be associated with recurrent respiratory tract infections.[2,49,50,51] As in nondwarfs, severe kyphoscoliosis can cause baseline hypoxemia and low lung volumes, which tend to worsen during sleep (or anesthesia).[52] In adult achondroplastic dwarfs, Stokes[53] demonstrated that it is the shape of the thorax that differs most compared with the anatomy of nondwarf individuals. The expansion of the uterus to become an intra-abdominal organ very early in gestation limits respiratory mechanics more in dwarfs than in women of normal stature. The additional decrease in FRC that occurs in pregnancy can worsen respiratory status in individuals with significant kyphoscoliosis.[20,54]

The mechanism of upper airway obstruction in achondroplasia is unclear. It may be due to mechanical factors such as brachycephaly (short head),[11] a flattened nasal bridge, facial hypoplasia, narrowed upper airways,[49] or a large tongue. Alternatively, it may be secondary to a functional problem such as hypotonia of airway muscles, which is seen in a generalized fashion in many achondroplastic dwarfs.[49] Sleep apnea probably has an obstructive mechanical origin in these patients as opposed to a central etiology.[43] Other respiratory difficulties relate to neurologic problems. For example, foramen magnum stenosis causing compression of a normal-sized medulla can result in apnea and respiratory embarrassment.[42] Increased ICP in an achondroplastic dwarf with hydrocephalus can also precipitate herniation through the abnormally small foramen magnum.[37,49,55]

Occasionally, cor pulmonale occurs as a consequence of these respiratory problems.[2,49,56,57] However, corrective procedures performed early in childhood may reverse this process. Stokes *et al.*[49] described an achondroplastic child with upper airway obstruction who experienced resolution of right-atrial and right-ventricular enlargement after undergoing adenoidectomy and tracheostomy. Unfortunately, this problem is unlikely to be reversible in patients with long-standing chest deformities and pulmonary hypertension who present for treatment while pregnant.

The nongravid achondroplastic dwarf has a reduced xiphoid to symphysis length as well as a decreased intercristal diameter (see Table 6.2). These decreased pelvic measurements, as well as the hyperlordotic features of achondroplasia, make the uterus an abdominal organ even prior to pregnancy. Uterine enlargement during pregnancy occurs in an exaggerated anterior and superior direction compared with parturients of normal stature.[1] By the fourth month, these patients appear to be in their 30th week of pregnancy.[1]

Pseudoachondroplasia

Three cases of pregnant patients with pseudoachondroplasia were noted in a survey of dwarfs.[14] No mention was made of anesthetic management or other complications encountered in

these parturients. Patients with pseudoachondroplasia typically present in early childhood, with similar stature to achondroplastic dwarfs, but no craniofacial abnormalities. They may have lumbar hyperlordosis, genu valgum ("knock knees"), genu varum (knees are abnormally separated and the lower extremities are bowed inwardly, i.e. bow leg),[11] and scoliosis. As adults, they usually are less than 130 cm tall.[2]

Nonachondroplastic dwarfism

Higher rates of spontaneous abortion, stillbirth, and premature delivery occur in nonachondroplastic dwarfs, as with dwarfs of proportionate short stature.[1]

Spondyloepiphyseal dysplasia

This is a rare form of dwarfism that is usually diagnosed at birth or in late childhood depending on the variant form. It arises either from a spontaneous mutation, or may be of X-linked or autosomal dominant inheritance.[58] These patients have a short trunk with normal or shortened limb length and are usually less than 130 cm tall.[2] The spondyloepiphyseal dysplasia *congenita* variant usually presents at birth and individuals may have short limbs,[2,58] whereas the spondyloepiphyseal dysplasia *tarda* variant is diagnosed in late childhood and limb length is usually normal.[2] Deformities in these patients include progressive kyphoscoliosis, pectus carinatum (prominent sternum), platyspondyly (congenital flattening of the vertebral bodies), central anterior pointing of the vertebral bodies, genu valgum, talipes equinovarus (foot deformity with plantar flexion of the foot and an inward turned heel), coxa vara (hip deformity with a decreased angle between the femoral head and neck and the axis of the femoral shaft), and odontoid hypoplasia.[2,11,59] They may also have visual problems, retinal detachment, deafness, and cleft palate.[2] Myer and Cotton[58] reported the presence of laryngotracheal stenosis in two dwarfs with spondyloepiphyseal dysplasia. This is an important finding for the anesthesiologist should patients require GA with the need for mask ventilation, direct laryngoscopy, and intubation. Odontoid hypoplasia can cause anterior dislocation of the first cervical vertebra producing spinal-cord compression.[60] The pelvis in this type of dwarfism is more contracted than in achondroplasia, with markedly reduced xiphoid to symphysis pubis and intercristal measurements (see Table 6.2).[1]

Spondylometaphyseal dysplasia

This is an extremely rare form of short-trunk dwarfism.[61] Features of concern include progressive kyphoscoliosis with spinal-cord compression, pectus carinatum, coxa vara hip deformity, contracted pelvis with narrowing of the sacrosciatic notches, and odontoid hypoplasia. Additionally, these patients may have cleft palate, hemangiomas, inguinal hernias, congenital hydronephrosis, and mitral valve prolapse.[19] Despite its rarity, two case reports exist of obstetric patients with this disorder. One received GA for C/S in the presence of hemorrhage and a marginal placenta previa[19] and one received combined spinal–epidural (CSE) anesthesia for elective C/S.[62]

Effects of pregnancy

Life expectancy is diminished and infertility is common in patients with osteochondrodysplasias.[1] However, pregnancy is not uncommon, particularly in achondroplasia. Many of the considerations related to pregnancy changes are the same as those described previously for proportionate dwarfs. However, because of their abnormal upper airway and thoracic anatomy, disproportionate dwarfs have a greater risk of cardiac and respiratory compromise earlier in gestation.

Obstetric management

There is some literature discussing obstetric concerns in this population,[14] but few reports describe anesthesia for pregnant osteochondrodysplastic dwarfs other than for achondroplasts.[4,59,62,63] Osteochondrodysplastic dwarfs are likely to need C/S, because their babies are often of relatively normal size and cannot be delivered safely through the small pelvis. Because inadequate pelvic capacity and other abnormal pelvic configurations prevent the head from engaging, breech and other malpresentations are frequent, making C/S the most common mode of delivery.[1]

Anesthetic considerations (see Table 6.5)

General overview

Because disproportionate dwarfs are at such high risk for C/S, the anesthesia service should be contacted early in gestation so that appropriate evaluation can be performed and an anesthetic plan developed prior to labor and delivery. A thorough history and physical examination is essential, paying special attention to head, neck, and airway anatomy, the range of flexion and extension of the neck, the presence of respiratory and neurologic signs and symptoms, and anatomical landmarks on the back.

If signs or symptoms of respiratory compromise are present, further investigations should be performed. Arterial blood gas analyses, pulmonary-function testing, and chest radiographs may be helpful in prescribing appropriate therapy to optimize pulmonary condition, as well as for use as a baseline for later in gestation and the postpartum period.[14,19] Some experts have recommended that all chondrodysplastic dwarfs have cervical spine flexion and extension radiographs prior to administration of anesthesia because of the high incidence of atlanto-axial instability and other upper cervical vertebral anomalies.[14,24] Certainly, *nonachondroplastic* disproportionate dwarfs should have these studies since a high percentage of them have C1 instability and the majority also have a myelopathy.[19,24,64,65] If symptoms suggesting spinal stenosis (e.g. neurologic symptoms or claudication) are present, imaging should be performed to rule out this diagnosis.

Some authors have recommended GA for C/S, citing fears that regional techniques may damage the spinal cord.[14] However, the

Table 6.5 Anesthetic considerations for disproportionate dwarfs

Characteristics	Anesthetic implications
Airway	
Large head, tongue, and mandible	
Maxillary hypoplasia	Possible difficult mask airway/ intubation
Limited neck extension	
Narrowed/obstructed upper airways	May need smaller ETT size
Neurologic	
Foramen magnum stenosis	Possible neurologic injury with laryngoscopy
Odontoid hypoplasia	Consider flexion/extension radiographs and/or awake fiberoptic intubation
Atlanto-axial instability	Possible neurologic injury
Musculoskeletal	
Spinal stenosis, lumbar hyperlordosis, thoracolumbar kyphosis, short stature	Technically difficult regional anesthesia More prone to neurologic injury
Smaller epidural space	Risk of dural puncture ↓Local anesthetic dose
Small abnormally shaped pelvis	High risk of cesarean section
Thoracic	
Chest deformities, hypoxia, hypercarbia, obstructive sleep apnea, cor pulmonale	Cardiac/respiratory compromise ↑Risk of respiratory depression with parenteral and neuraxial opiates
Uterine impingement on intrathoracic structures	May not tolerate supine position and i.v. fluid administration
Abdominal	
Early intra-abdominal uterine location	↑Risk of aspiration ↑Risk of supine hypotension

same authors acknowledge that GA has "a higher risk of complications compared with spinal and epidural anesthesia."[14] In one survey of 70 pregnancies in dwarfs, 63 patients were delivered by C/S. The other 7 patients, all of whom had a chondrodystrophy of unknown etiology, were delivered vaginally. General anesthesia was used in the majority of surgical cases, although 23 patients received successful epidural anesthesia, 12 of whom were achondroplastic dwarfs.[14] Regardless of the technique planned, it is important to remember that the uterus is an extrapelvic organ in these patients and its enlargement increases the incidence and severity of supine hypotension.[20,21] Left uterine displacement, cautious intravascular fluid management, and prompt and aggressive pressor support after regional block are indicated. If a GA is chosen, there is the increased aspiration risk present in all parturients undergoing GA, as well as additional risk secondary to uterine impingement on the dwarf's abdominal contents.[66,67]

Anesthesia for achondroplastic parturients

The current literature reveals several descriptions of anesthetic management for achondroplastic dwarfs.[20,21,26,28,54,68,69,70,71,72,73,74,75,76] General and regional anesthesia both pose potential hazards in these patients and the choice should be individualized to each patient. The factors that increase anesthetic risk are detailed in Table 6.5. Routine intraoperative monitoring is sufficient for patients without pulmonary compromise. If respiratory embarrassment is present, an intra-arterial catheter assists in monitoring oxygenation, ventilation, and acid-base status. Two reports have mentioned difficulty with the accuracy of noninvasive blood pressure monitoring in achondroplastic dwarfs because of their short, yet often obese, arms.[21,69] In one instance, intra-arterial catheter placement was necessary to accurately measure blood pressure in a previously hypertensive parturient.[69]

A serious concern is the risk of difficult intubation. The large head with facial hypoplasia and a large mandible, limited neck extension, and cervical instability are important considerations.[25] While the majority of reports do not describe airway difficulties in achondroplastic dwarfs, there are enough cases of airway problems to mandate extreme caution.[26,28] Awake direct laryngoscopy or fiberoptic laryngoscopy[76] are options to be considered when a GA is planned. One option is to evaluate the laryngeal view preoperatively in the awake patient at a preoperative evaluation using gentle direct laryngoscopy after application of topical anesthesia, and minimal sedation if needed.[4,20] This may facilitate the prediction of ease of intubation should it become necessary in an urgent situation (when fiberoptic intubation would be too time-consuming). If this examination is done in the operating room then intubation can be performed and GA induced immediately thereafter. If a patient is suffering from pulmonary compromise prior to C/S, she may be unable to tolerate the supine position while awake. Additionally, rapid fluid loading administered prior to institution of regional anesthesia may not be well tolerated, so fluids should be given cautiously rather than in large, predetermined volumes. Individuals with significant pulmonary insufficiency may benefit from endotracheal intubation and mechanical ventilation during surgery and the postpartum period.

As with proportionate dwarfs,[24] ETT size is thought to be best predicted in achondroplastic dwarfs by weight rather than age.[25] However, most studies consist primarily of pediatric patients. In the five adults intubated in the report by Mayhew *et al.*[25] all patients over the age of 17 were intubated with either a 7.0 or 7.5 mm cuffed ETT. In four case reports of GA for C/S in achondroplastic patients, a 6.5 mm ETT was used once, a 7.0 mm tube was used twice, and tube size was not reported in one case.[20,54,69,70] It seems prudent to have numerous ETT sizes available for the parturient dwarf as the airway changes induced by pregnancy, including airway edema, may necessitate the use of a smaller than expected tube.[13]

Regional anesthesia is a viable option in many achondroplastic patients, particularly if neurologic symptoms are absent. However, abnormal spinal anatomy may give rise to more patchy blocks and a higher rate of dural puncture, technical difficulty, and a greater potential for spinal-cord injury. Nevertheless, a regional anesthetic may be a better choice than GA for many individuals.[14,15] In one

Table 6.6 Epidural anesthesia for achondroplastic dwarfs for cesarean section

Patient height & weight	Epidural level	Local anesthetic	Volume	Sensory level	Author	Complication
122 cm 57 kg	L2–3	3% 2-chloroprocaine	9 ml + 9 ml later	T4	Cohen, 1980	Difficulty threading catheter. Inadvertent dural puncture at L3–4
120 cm 48 kg	L2–3	0.75% plain bupivacaine	21 ml	T3–4	Waugaman, 1986	Transient paresthesia with catheter placement.
121 cm 73 kg	L2–3 ?L3–4	0.5% plain bupivacaine	12 ml + 11 ml saline	C5	Brimacombe, 1990	Difficulty threading catheter: i.v. difficulty with 2nd attempt, but successful.
111 cm 46 kg	L2–3	0.5% plain bupivacaine	5 ml	T4 on the left T6 on the right	Wardall, 1990	
119 cm 61 kg	T11–12	2% lidocaine + 1:200 000 epinephrine	8 ml	T5	Carstoniu, 1992	
120 cm 64 kg	L3–4	2% lidocaine + 1:200 000 epinephrine	13.5 ml	T4	Morrow, 1998	

Modified with permission from Carstoniu, J., Yee, I. & Halpern, S. Epidural anaesthesia for Caesarean section in an achondroplastic dwarf. *Can. J. Anaesth*. 1992; **39**: 708–11.

Table 6.7 Epidural test doses in pregnant patients with achondroplasia

Author	Test dose
Cohen, 1980[20]	3 ml 3% 2-chloroprocaine
Brimacombe, 1990[21]	2 ml 0.5% plain bupivacaine
Wardall, 1990[71]	3 ml 0.5% plain bupivacaine
Carstoniu, 1992[68]	1 ml 2% carbonated lidocaine with 1:200 000 epinephrine
Morrow, 1998[74]	1.5 ml 2% lidocaine with 1:200 000 epinephrine

series eight achondroplastic dwarfs received six spinal or epidural anesthetics without neurologic sequelae, although technical difficulty was frequently encountered.[24] The details of five reports of continuous epidural anesthesia for C/S are outlined in Table 6.6. Although some technical difficulties occurred, all patients had successful epidural anesthesia without neurologic sequelae.[20,21,68,71,74,77] Some patients underwent multiple attempts at epidural placement: one patient had an inadvertent dural puncture, and one had an intravascular catheter, which was recognized and then replaced with some difficulty.[20,21,74]

All but one of the patients presented in Table 6.6 required a decreased dosage for appropriate surgical level of anesthesia compared with nondwarf individuals. A continuous regional (spinal or epidural) technique is preferred to a single-shot spinal technique for this reason, since no dosage guidelines are available for patients with short stature and abnormal spinal anatomy. With a single-shot technique, fears of overdosage may lead to inadequate anesthesia and intraoperative patient discomfort while excessive dosage can cause high spinal or epidural block. Careful evaluation of the upper and lower level of epidural block should be made before incision to ensure adequate surgical anesthesia, with supplemental local anesthetic administered as necessary. Because failed or high block can complicate regional anesthesia, preparations should always be made for management of a difficult airway including availability of all necessary equipment.

Epidural test doses used in the reported cases have been quite variable (see Table 6.7).[20,21,68,71,74] While no guidelines exist for the optimal test dose, the amount of local anesthetic injected should be large enough to detect a subarachnoid catheter without inducing high or total spinal anesthesia.[68] Since these patients have abnormal spinal and epidural anatomy, the dose of epinephrine and local anesthetic is not known for any one individual. One patient received epinephrine, 5 μg, in the test dose.[68] However, this may not be adequate to detect intravascular placement compared to the more accepted test dose of 15 μg.[18] Unlike the proportionate short-statured patient, a dosage based on weight may not be appropriate, especially since the spinal cord of an achondroplastic dwarf is larger in relation to their spinal canal.

Single-shot spinal anesthesia for emergency C/S is mentioned in one report in which 1.3 ml of 0.5% hyperbaric bupivacaine and 10 μg

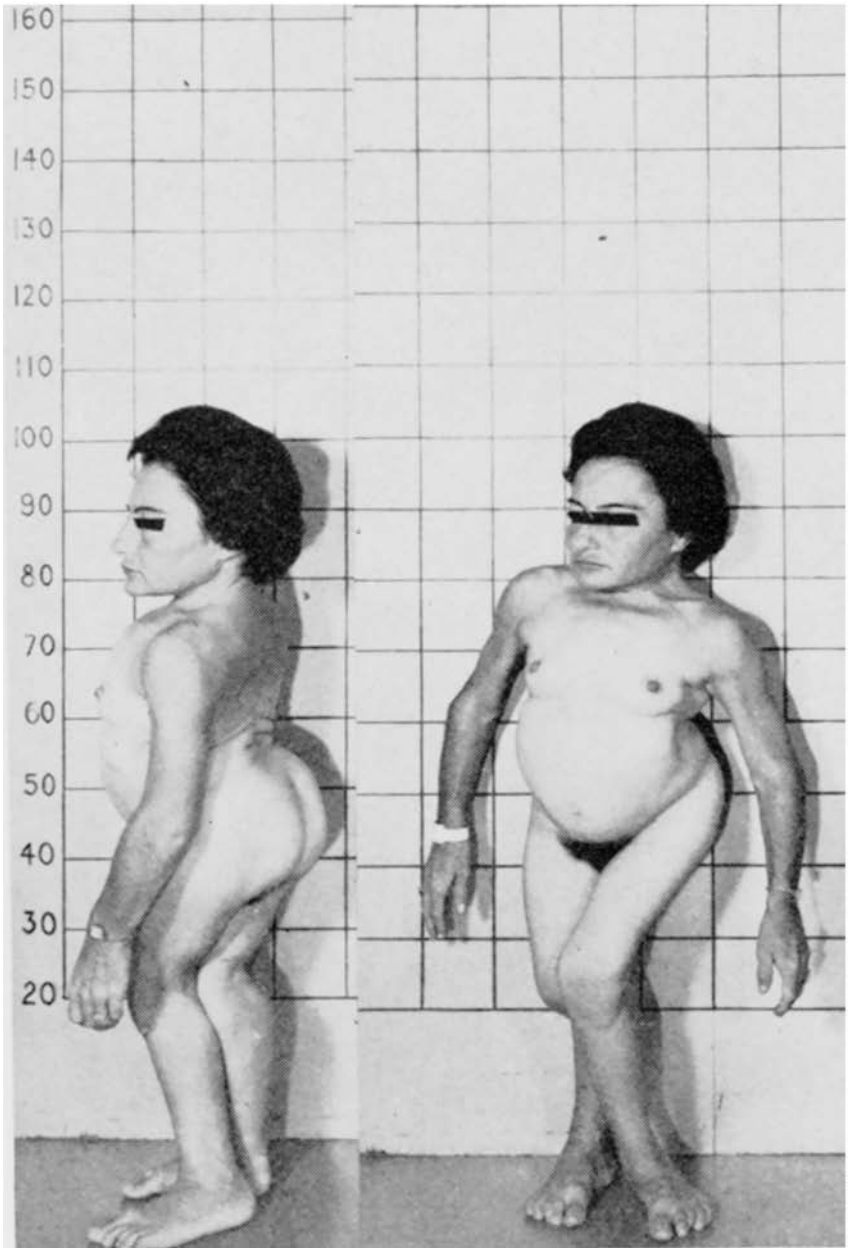

Figure 6.3 Spondyloepiphyseal dysplasia (Patient F. L.) – deformities of spine and limbs with contracture of the pelvis and kyphoscoliosis. Reprinted with permission from C. V. Mosby Co. from Tyson, J. E., Barnes, A. C., McKusick V. A. *et al*. Obstetric and gynecologic considerations of dwarfism. *Am. J. Obstet. Gynecol*. 1970; **108**: 688–703.

of fentanyl were administered via a 26-gauge needle to obtain a bilateral block to T3.[73] The patient had significant hypotension minutes after the spinal injection, which responded to ephedrine 15 mg and a 250 ml fluid bolus with no subsequent episodes of hypotension. Combined spinal–epidural anesthesia was used by Trikha *et al*. for vesico-vaginal fistula repair in a nonpregnant achondroplastic dwarf, and could be used for urgent C/S.[75] However, the disadvantages may be similar to single-dose spinal anesthesia with regard to rapid onset of block and hypotension, and potential for neurologic damage because of anatomic abnormalities.

One brief report describes a successful continuous spinal anesthetic in a pregnant achondroplastic dwarf.[72] A 32-gauge microspinal catheter (withdrawn from use in the United States by the Food and Drug Administration because of concerns over associated neurologic deficits)[78,79] was used. A continuous spinal technique using a 20-gauge epidural catheter may be a good alternative either electively or if inadvertent dural puncture occurs while attempting epidural catheterization.

Postoperative pain management with neuraxial opioids was mentioned in only one report, where epidural diamorphine in a 2.5 mg dose was administered every 12 hours.[21] There was no mention of postoperative monitoring in this report. Although a single dose of epidural morphine is the usual practice in our institution, a reduced dosage with increased postoperative respiratory monitoring (such as hourly respiratory monitoring and continuous pulse oximetry) seems appropriate. With this proviso, epidural morphine can be used safely in parturients of short stature. Careful monitoring of neurologic function is also

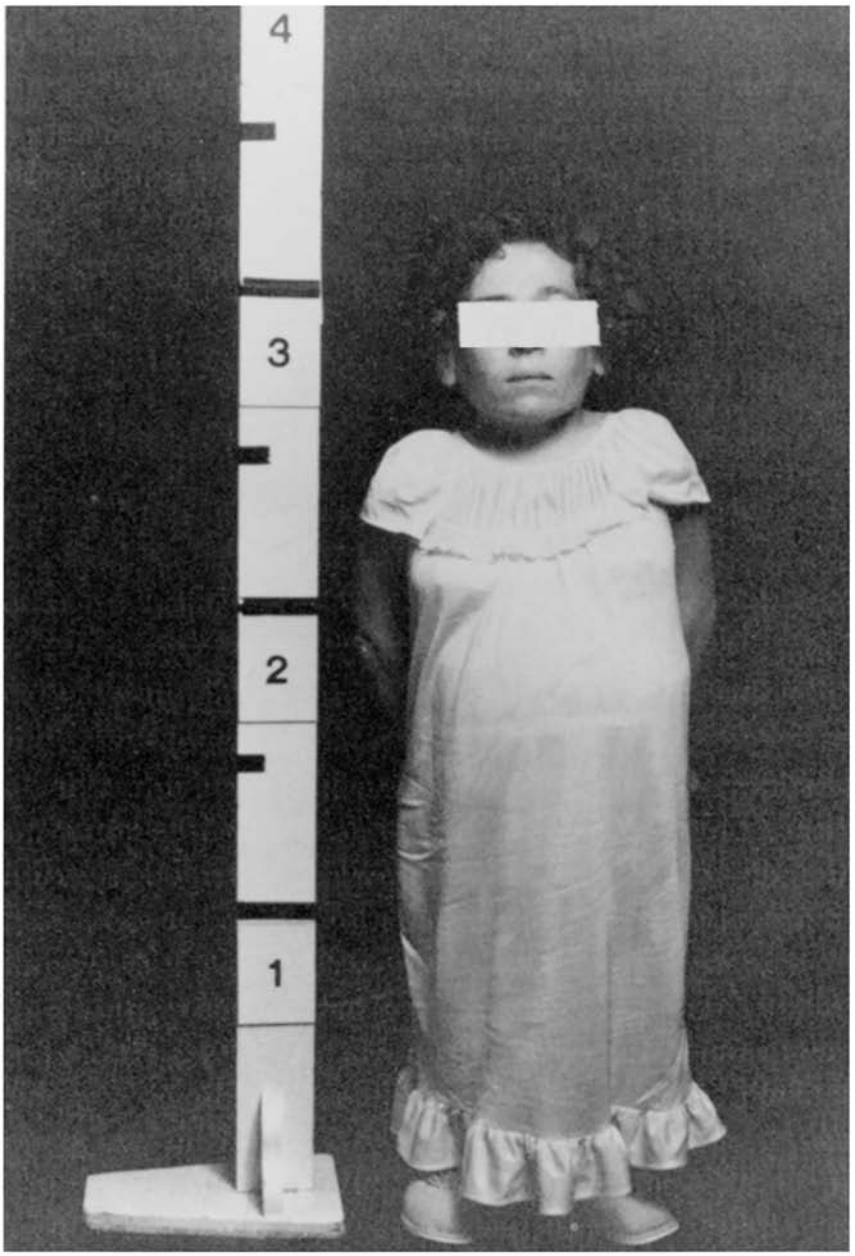

Figure 6.4 Patient with spondylometaphyseal dysplasia two days postpartum. Note short stature, short neck. Reprinted with permission from J. B. Lippincott Co. from Benson, K. T., Dozier, N. J., Goto, J. *et al.* Anesthesia for cesarean section in patient with spondylometepiphyseal dysplasia. *Anesthesiology* 1985; **63**: 548–50.

advisable in the postoperative period as the spinal stenosis and decreased epidural space capacity may result in raised epidural pressure and decreased spinal-cord perfusion.

Anesthesia for nonachondroplastic disproportionate parturients

The anesthetic considerations for the nonachondroplastic disproportionate parturient are similar to those with achondroplasia. Most of these patients will need a C/S for obstetric reasons. Craniofacial deformities may be present, so the anesthesiologist should anticipate airway difficulties. Because problems may also result from atlantoaxial instability, *preoperative flexion-extension cervical spine X-ray and possibly CT scan is warranted in all patients*.[65] A patient with spondyloepiphyseal dysplasia congenita[65] developed massive pyramidal tract signs consisting of spastic tetraparesis, increased reflex activity, and intact sensation following direct laryngoscopy. This patient subsequently died from complications related to surgical correction of the cervical spine compression, leading some to advocate fiberoptic intubations for all patients with nonachondroplastic disproportionate dwarfism.[76] Cardiac or pulmonary compromise may be present, depending on the presence of preexisting thoracic spinal deformities and the degree of uterine impingement on intrathoracic structures. Cardiac anomalies may be present in some forms of dwarfism, thus any symptoms suggestive of cardiac disease should be investigated prior to delivery. As in achondroplasia, other spinal deformities can exist making regional anesthesia more difficult.

Four case reports describe the anesthetic management in parturients with nonachondroplastic disproportionate dwarfism.[4,19,62,63] Two describe patients with spondyloepiphyseal dysplasia congenita who had a C/S under epidural anesthesia. The first patient had cervical spine abnormalities and marked thoracic kyphoscoliosis and lumbar lordosis (see Figure 6.3).[63] After inadvertent i.v. placement of an epidural catheter, repeat placement was uneventful; 8 ml of 2% lidocaine with 1:200 000 epinephrine was administered for a surgical block to T4[63] The second patient underwent in vitro fertilization, resulting in a twin pregnancy.[4] While she did not have any cervical spine abnormalities, she did have marked kyphoscoliosis and vertebral flattening. She underwent uneventful epidural anesthesia with a total of 8 ml of 0.5% bupivacaine with 1:200 000 epinephrine (sensory level of T5) and used i.v. patient-controlled analgesia for postoperative pain management.

Two published reports exist describing the anesthetic management of parturients with spondylometaphyseal dysplasia.[19,62] The first involved an emergency C/S performed for vaginal bleeding in a parturient with a marginal placenta previa (see Figure 6.4).[19] This woman had limited neck and jaw mobility and was thought to have "a very high anterior larynx." She underwent awake direct laryngoscopy, which revealed the epiglottis and posterior arytenoids. The authors then performed a rapid sequence induction with easy endotracheal intubation. The case was complicated not only by blood loss, but also by the presence of pulmonary edema, probably secondary to ritodrine administration.[19] However, no anesthetic complications occurred.

The second report described a woman with spondylometaphyseal dysplasia who had a CSE for an elective C/S.[62] The spinal dose was 1.4 ml of 0.5% hyperbaric bupivacaine with fentanyl 10 μg, which yielded a T7 level after 10 minutes. She then received 1 ml of 0.5% bupivacaine through the epidural catheter, producing a T4 level five minutes later. Epidural diamorphine 2.5 mg, and diclofenac 100 mg rectally, were given for postoperative analgesia, with 16 hours of postoperative respiratory monitoring and no complications reported.[62]

Neonatal considerations

Many types of dwarfism can be diagnosed immediately after birth. The incidence of newborn dwarfism in this population greatly depends on the parents' type of dwarfism and the accuracy of the diagnosis.[1] The prognosis for each infant is dependent on the type of dwarfism the infant exhibits. For example, infants who are homozygous for the achondroplasia gene either die in utero or the early neonatal period. Infants with other types of dwarfism may have thoracic cage abnormalities with respiratory compromise necessitating ventilatory support. The neonatal team should be notified in advance so that appropriate preparation can be made for the resuscitation of a potentially compromised baby.

Other types of dwarfism

While the types of dwarfism discussed in this chapter are those most commonly encountered in parturients, there are other causes of short stature. A patient with Marshall-Smith syndrome miscarried at 19 weeks' gestation. Her mother also had Marshall-Smith syndrome. This condition is associated with laryngomalacia and respiratory compromise, making GA especially difficult should patients with this disorder carry their pregnancies to term.[80] Successful pregnancies in patients with conditions thought to be incompatible with pregnancy continue to be reported. One report of pregnancy in a patient with diastrophic dwarfism exists.[81] This patient had an extremely deformed vertebral column and severe restrictive pulmonary disease. While details about the anesthetic and airway management are not included, she had a C/S under GA at 26 weeks' gestation. One report of a successful pregnancy in a patient with Cockayne syndrome describes the patient being delivered by C/S, but anesthesia is not mentioned.[82] There is also a report of two patients with severe osteogenesis imperfecta.[5] Both patients were delivered by C/S, one managed with epidural anesthesia and the other with awake fiberoptic intubation and GA, due to her inability to tolerate the supine position.[5] There is also a report of a patient with Larsen syndrome who underwent uneventful epidural anesthesia for C/S.[83]

As individuals with different types of dwarfism marry and have children, mixed type dwarfism will become more common. We encountered a patient with mixed achondroplastic and ateliotic dwarfism who was married to a dwarf with an unspecified type of chondrodysplasia. She had a C/S at 37 weeks' gestation under uneventful epidural anesthesia, delivered a 7 lb 6 oz (3345 g) baby, and received 3 mg epidural morphine for postoperative pain with no complications.

Summary

Currently, relatively few reports are available in the literature to guide the anesthetic management of parturients of short stature. All pregnant dwarfs are at high risk for C/S so anesthesia will be needed. The physiologic changes of pregnancy often exacerbate the preexisting mechanical and physiologic abnormalities present in dwarfs increasing the risk from anesthesia. Since numerous forms of dwarfism exist, it is critical that each parturient be evaluated early in pregnancy and her individual needs assessed prior to anesthetic intervention. Accommodations for the logistics of short-stature must be considered for the patient and sometimes a short-statured partner, including obtaining smaller chairs, step-stools, and placing the patient's bed at a lower level. The patient with short-stature desires a compassionate and safe birth experience and an effort must be made by the anesthesia team to provide individualized care and communication.

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7 DISORDERS OF THE VERTEBRAL COLUMN

Edward T. Crosby

Introduction

Symptoms relating to the musculoskeletal system are among the most common complaints registered by pregnant women. The maternal axial skeleton is subjected to considerable gestational changes and stresses and skeletal anomalies, both congenital and acquired, may impact on the process and outcome of gestation and labor. Among the most important of these anomalies is *scoliosis*, arising either as the idiopathic form or as a result of an underlying neuromuscular disorder.

Other syndromes are less commonly encountered: these include *disc prolapse*, *osteoporosis of pregnancy*, and *spondylolysis* and *spondylolisthesis*.

Scoliosis

Moderate to severe scoliotic curves are not common in women of childbearing age. The major reason for this is that screening programs identify many at-risk women early in the disease process, resulting in timely intervention and curve correction. Additionally, primary neuromuscular diseases that result in scoliosis are relatively rare and may themselves limit a woman's reproductive potential. Despite the fact that women with moderate to severe scoliosis constitute a small population of obstetric patients, pregnancy within this population is common. The process and outcome of pregnancy, labor, and delivery are often similar in women with scoliosis compared with the general population. However, if the disease process is advanced, pregnancy and labor may not only be complicated, but also life-threatening. In this small subpopulation, a detailed understanding of the pathophysiology of advanced scoliosis and the interaction with pregnancy is necessary to provide effective maternal care.

Definition and description

Scoliosis is defined as an appreciable lateral deviation in the normally straight vertical axis of the spine. Scoliosis can be classified according to its cause and by a description of the curve, including the magnitude, location, and direction.[1] Scoliosis is divided into *structural* and *nonstructural* types, on the basis of spinal flexibility. Nonstructural curves are those seen in postural scoliosis or those related to sciatica or leg length discrepancies. Nonstructural curves are occasionally seen in parturients, developing with progression of the gestation and resolving after delivery. They do not affect the mobility of the spine; they are nonprogressive and resolve with attention to the underlying cause. Structural curves are those of idiopathic scoliosis or resulting from the conditions outlined in Table 7.1. Reduced spinal mobility is characteristic of the structural curves as is asymmetry in lateral flexibility, which is best appreciated on left- and right-bending x-ray films. Structural curves are associated with a fixed prominence, the rib hump, on the convex side of the curve. This prominence is best demonstrated in the forward-bend position. Kyphoscoliosis, a combination of kyphosis and scoliosis, is uncommon in parturients. It is usually a congenital disorder, although it may be related to progressive infantile scoliosis or paralytic forms of scoliosis.

The curve of scoliosis is typically described by its angle, location, and direction. The curve angle is determined by the Cobb method, in which the upper and lower end vertebrae of the curves are identified. Lines are drawn through the end points of these vertebrae and the Cobb angle is formed by the intersection of perpendiculars to these lines (see Figures 7.1 and 7.2). The Cobb angle is used to follow progression of the curve and to determine the requirement for, and nature of, an intervention. The anatomic area of the spine in which the apex of the curve is situated determines the location of the curve. Thoracolumbar curves are seen most commonly, followed in frequency by those affecting only the thoracic or lumbar spines.[2] The lower limit of curves involving the lumbar spine is usually L3 or L4, although relatively few curves extend this far caudad. The direction assigned to the curve is determined by the convexity. Right thoracic curves are the most common curves described in idiopathic scoliosis.

Etiological considerations

The cause of the majority (85–90%) of cases of scoliosis is unknown and these are characterized as idiopathic. Idiopathic scoliosis is divided into three types: *infantile*, *juvenile*, and *adolescent*.[1] The majority of infantile scoliosis do not progress beyond 30° and resolve spontaneously. Less commonly, and usually in males, the infantile curves are "progressive" resulting in severe deformity early in life. Juvenile scoliosis has its onset in the four- to nine-year age group, is less common than the adolescent form, and is not as well defined. Adolescent idiopathic scoliosis (AIS) has its onset between age ten and the age of skeletal maturity and represents the most common form of idiopathic scoliosis. It usually occurs in an otherwise healthy child, often in association with a family history of the disease. The inheritance pattern is consistent with a dominant inheritance with reduced penetrance.[3]

Less common causes of scoliosis are listed in Table 7.1. Of these rarer forms, the most common in parturients are deformities caused by neurological and myopathic conditions that result in

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Table 7.1 Conditions associated with scoliosis

Congenital (vertebral) anomalies
Hemivertebra
Spina bifida
Neurologic disorders
Spinal muscular atrophy
Cerebral palsy
Polio
Neurofibromatosis
Myopathic disorders
Myotonic dystrophy
Muscular dystrophy
Connective tissue disorders
Marfan syndrome
Rheumatoid disease
Osteochondystrophies
Achondroplasia/hypochondroplasia
Osteogenesis imperfecta
Osteoporosis of pregnancy
Infection
Tuberculosis
Posttraumatic

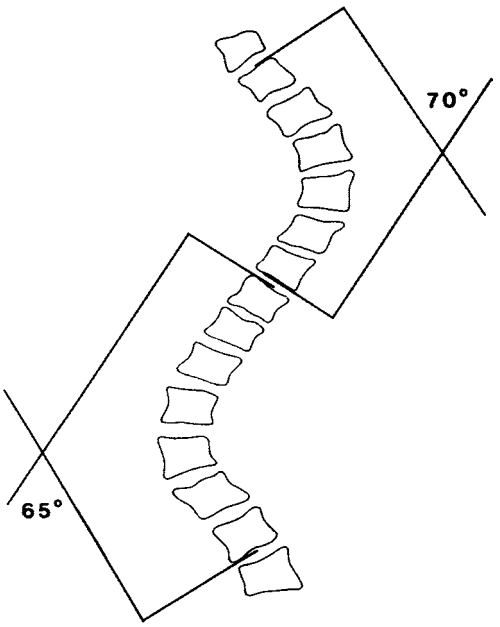

Figure 7.1 Cobb angle – schematic representation. A line is drawn parallel to the superior cortical plate of the proximal end vertebrae and to the inferior cortical plate of the distal end vertebrae. A perpendicular line is erected to each of these lines. The angle of intersection is the (Cobb) angle of the curve. (From Crosby, E. T. Musculoskeletal disorders. In Chestnut, D. H. (ed.), *Obstetric Anesthesia: Principles and Practice*, 3rd edn. Philadelphia, PA: Elsevier Mosby, 2004, p. 859.)

paralytic scoliosis as well as curves resulting from osteochondystrophies. Infectious causes of scoliosis, predominantly tuberculosis related, are reported primarily from underdeveloped countries.[4] Scoliosis may also result from vertebral fractures, occurring as a consequence of pregnancy-associated osteoporosis, but reports of this syndrome are rare.[5]

Incidence and prevalence

The prevention of poliomyelitis and the low prevalence of other conditions leading to scoliosis mean that surveys of scoliosis largely reflect the incidence and prevalence of AIS.[3] The incidence of minor curves in the US population as assessed by x-ray is 4 in 1000.[6] The incidence of deformities that reach angles of 35° is 1 in 1000, and of deformities greater than 70°, approximately 0.1 in 1000.[7] These larger curves occur predominantly in females. The reported prevalence of scoliosis ranges from 0.3 to 15.3%.[8] Although the prevalence in the American population is 1.8%, if minor curvatures (5–10°) are included, the rate in adult females is closer to 10%.[9,10] Scoliosis screening programs and early interventions are advocated to prevent the natural progression of the disease. Evidence suggests a reduction in the incidence of uncorrected major curves in adults, likely due to early diagnosis and intervention.[11]

Severe scoliosis is rare in parturients and this rarity probably results from the relatively low prevalence of moderate to severe curves in the population, because pregnancy is common in women who have scoliosis. In a postal survey of women diagnosed with scoliosis in Minnesota, 72% of responders had been pregnant an average of 2.8 times each.[12] Most of these women (68%) had idiopathic scoliosis with the majority adolescent-onset disease. Their mean curve size was 37°, and most of the spinal curves (61%) were thoracic or thoracolumbar. Fifty-eight percent of the patients had undergone spinal surgery for scoliosis, which may account for the relatively small Cobb angles in the group. Three reviews confirmed that pregnancy is common in women with scoliosis.[13,14,15] There were no important differences between the groups with respect to the likelihood of marriage, number of pregnancies, incidence of gestational back complaints, or the requirement for cesarean section (C/S).

Risk factors for curve progression

Progression of a curve is defined as an increase of 5° or more, as measured by the Cobb method, over subsequent assessments. Progression is most likely to occur in the rapid adolescent growth phase in immature patients; in patients with larger curves (>20°) at the time of original diagnosis; and in patients with double curves at presentation.[16] There is a threefold increase in the risk of progression if the initial curve is measured at >20° than if the curve is <20°, and thoracic curves are more likely to progress if the Cobb angle is large (> 50°).

Although it was once thought that there was little progression after skeletal maturity in untreated patients, observation over decades has shown that moderate curves (60–80°) increase an average of 30°.[17] The natural history of the untreated severe curve is progression of the deformity over time, resulting in early death from cardiopulmonary failure.[3,17,18] Long-term follow-up of patients with major, uncorrected curves demonstrated

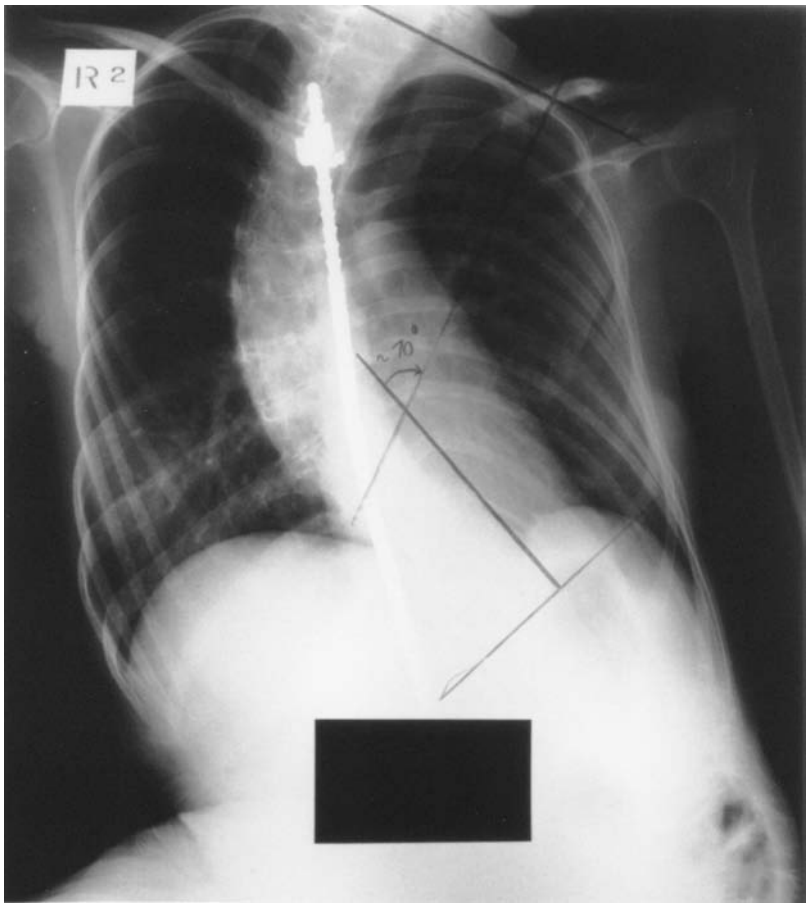

Figure 7.2 Cobb angle – chest x-ray. Cobb angles are represented on this x-ray of a young woman with a progressive spinal muscular atrophy (Kugelberg-Welander syndrome) and a 70° thoracic curve. Note should also be made of the rib separation on the right hemithorax compared with the left. This patient's pelvic film is detailed in Figure 7.6.

that the mortality rate was twice that of the general population, and the average age at death was 46.6 years.[19]

Skeletal changes in idiopathic scoliosis

The skeletal anatomic pathology that results from AIS is complex. Deformation of vertebrae is present when Cobb angles are >40°, as are abnormal relationships between vertebrae, excess curvature in the frontal plane, loss of normal sagittal plane curves, and rotation in the vertical axis.[20] The vertebral bodies have shorter, thinner pedicles and laminae on the concave side and a narrower vertebral canal (See Figure 7.3). The transverse processes are anatomically abnormal and asymmetric in their spatial orientation. The spinous processes are deformed and skewed from the midline.

The rotatory component associated with the scoliotic curve is such that the axial rotation of the vertebral body is typically into the convexity of the lateral curve, and the spinous process is rotated back into the concavity (see Figure 7.4A).[21] As a result of the rotation of the vertebrae, the ribs on the side of the convexity are pushed backward, producing a prominent posterior angle – the rib hump (see Figure 7.4B). The interlaminar space is shifted more toward the curve convexity than is the spinal process, and the usual anatomic relationship between these structures is altered. This change is important if major neuraxial block is considered, because the underlying structures no longer maintain the same relationships to surface landmarks.

Indications for intervention and principles of corrective surgery

The goal of surgery is to fuse the spinal curve and prevent progression of the deformity. Modern surgical techniques consistently yield a 50% reduction of the deformity, without excessive risk. The area fused should be kept as short as possible to maintain the greatest number of mobile articulations, but enough of the spine must be fused to stabilize the deformity. The most common stabilization technique remains the posterior fusion and instrumentation. Common to all the techniques described is the requirement for spinal instrumentation and extensive bone grafting in the axial spine (see Figure 7.5).

Follow-up studies of patients who underwent early operative corrections of severe scoliotic curves demonstrated either improvement in lung volumes and function, or the progression of the restrictive lung disease has been arrested postoperatively.[22,23,24] Improved function was demonstrated when significant reductions in moderate to severe curves were achieved with Harrington instrumentation or when thoracic kyphosis was

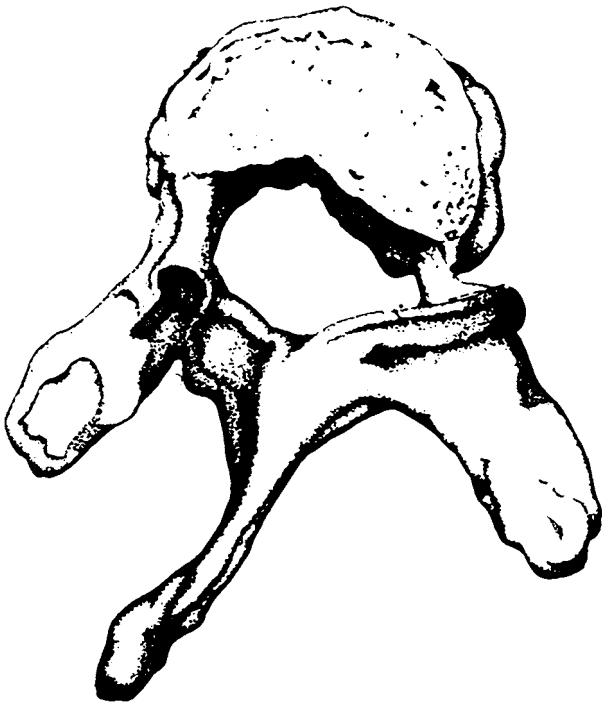

Figure 7.3 Scoliotic deformation of the vertebral body. The vertebra diagrammed is from a spine with a moderate to severe right-sided curve. The body has shorter, thinner pedicles on the concave (left) side and a narrower vertebral canal. The transverse processes are abnormal and asymmetric in their spatial orientation. The spinous process is deformed and skewed from the midline. (See also Figure 7.7.)

normalized.[25,26] Delaying correction until adulthood appears to reduce the gains made in lung function, when compared with results of earlier correction.[27] Patients who undergo early instrumentation generally do not develop the cardiopulmonary complications that afflict patients with severe and uncorrected disease.[22,23,27,28,29]

Cardiopulmonary pathophysiology in idiopathic scoliosis

Respiratory pathophysiology

Scoliosis interferes with the formation, growth, and development of the lungs.[30] Because the number of alveoli increase greatly between birth and age eight, the occurrence of scoliosis before lung maturity reduces the number of alveoli formed. The pulmonary vasculature forms in parallel with the alveoli and is likewise affected, resulting in increased pulmonary resistance, pulmonary hypertension, and, in severe cases, right heart failure. The pulmonary pathophysiology of scoliosis also includes the effects of the vertebral and ribcage deformity on the mechanical function of the lung. The key findings that correlate with respiratory compromise are (1) a thoracic curve; (2) thoracic lordosis; and (3) a ribcage deformity. The most common abnormality is a restrictive pattern of pulmonary dysfunction with a reduction in lung volume and compliance. This pattern is seen in all patients with thoracic curves $> 65^{\circ}$. Ventilatory reserve is limited, resulting

(a)

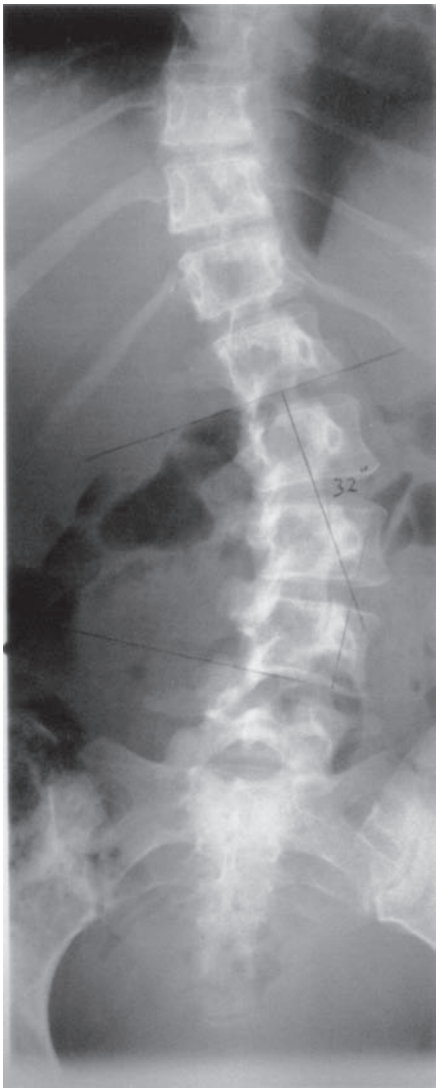

Figure 7.4 Idiopathic scoliosis – lumbar spine. (A) X-ray study of the lumbar spine in a 26-year-old woman with idiopathic scoliosis. The spinous process and pedicles are rotated away from the curve convexity and into the concavity. The epidural space was entered easily by directing the needle about 15° off the perpendicular at the skin level toward the convexity of the curve. (From Crosby, E. T. Musculoskeletal disorders. In Chestnut, D. H. (ed.), *Obstetric Anesthesia: Principles and Practice*, 3rd edn. Philadelphia, PA: Elsevier Mosby, 2004, p. 860.) (B) Rib hump – schematic. As a result of rotation of the vertebrae, the ribs on the side of the convexity are pushed backward, producing the prominent posterior angle, the rib hump. The intercostal gap is increased in the hemithorax with the rib hump. (See Figure 7.2.)

in dyspnea on exertion and reduced exercise capacity in the early stages. Progression of the curve results in greater respiratory compromise.

Although the residual volume (RV) is generally not affected in most patients with restrictive lung disease, functional residual capacity (FRC) is decreased. If the FRC is sufficiently reduced, airways may close during normal tidal breathing, resulting in ventilation/perfusion (V/Q) mismatch and arterial hypoxemia.

(b)

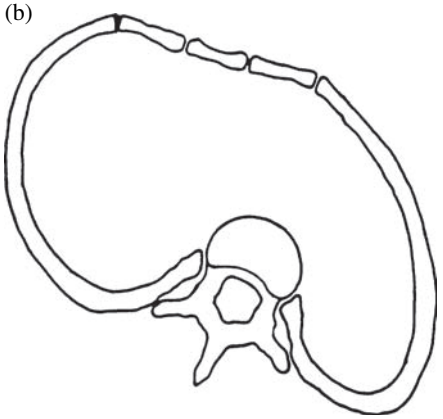

Figure 7.4 cont.

Total lung capacity (TLC – the volume of the lung at end-maximal inspiration) and vital capacity (VC – the volume that can be exhaled from the lungs starting from maximal inspiration) are also both reduced. Normal VC in adults is 70 to 80 ml/kg. When VC is reduced to < 15 to 18 ml/kg, expiratory airflow may become inadequate to produce an effective cough. Flow rates, as measured against lung volumes, provide a measure of the presence or absence of airway obstruction. These ratios tend to be unaffected in restrictive lung disease, implying that intrinsic airways disease is not typically associated with scoliosis.

The work of breathing depends on many factors, the most important of which are the stiffness of the lungs and chest wall and the resistance to flow through the airways. In patients with thoracic scoliosis, the chest wall is stiff, larger transpulmonary gradients must be generated to achieve airflow and more work is necessary to expand the lungs to any volume. The actual work done is reduced if patients with scoliosis breathe more rapidly at smaller volumes. However, a normal dead space in conjunction with small-tidal-volume breathing results in increased wasted ventilation. Increased ventilatory requirements may result in a large increment in respiratory work and as the respiratory work increases, the potential for respiratory failure increases. If the respiratory muscles are forced to work at a sustained intensity of > 40% of maximum, muscle fatigue and respiratory failure result.[31]

Dyspnea on exertion occurs before the onset of alveolar hypoventilation. The degree of spinal deformity usually correlates with symptom severity. Cardiorespiratory symptoms are not common with curves < 70°. Dyspnea is more common as the deformity exceeds 100°, and alveolar hypoventilation occurs when angles exceed 120°. In younger patients with moderate thoracic scoliosis (25–70%), impaired exercise capacity is usually due to deconditioning and lack of regular aerobic exercise, not to intrinsic ventilatory impairment.[32] Patients with severe scoliosis (curve > 90°) are more likely to experience sleep-breathing abnormalities, night-time hypoxemia, and daytime hypercapnia.[33]

Cardiovascular pathophysiology

Scoliosis and cardiac anomalies may have a common embryologic etiology.[34] In AIS, the incidence of mitral valve prolapse

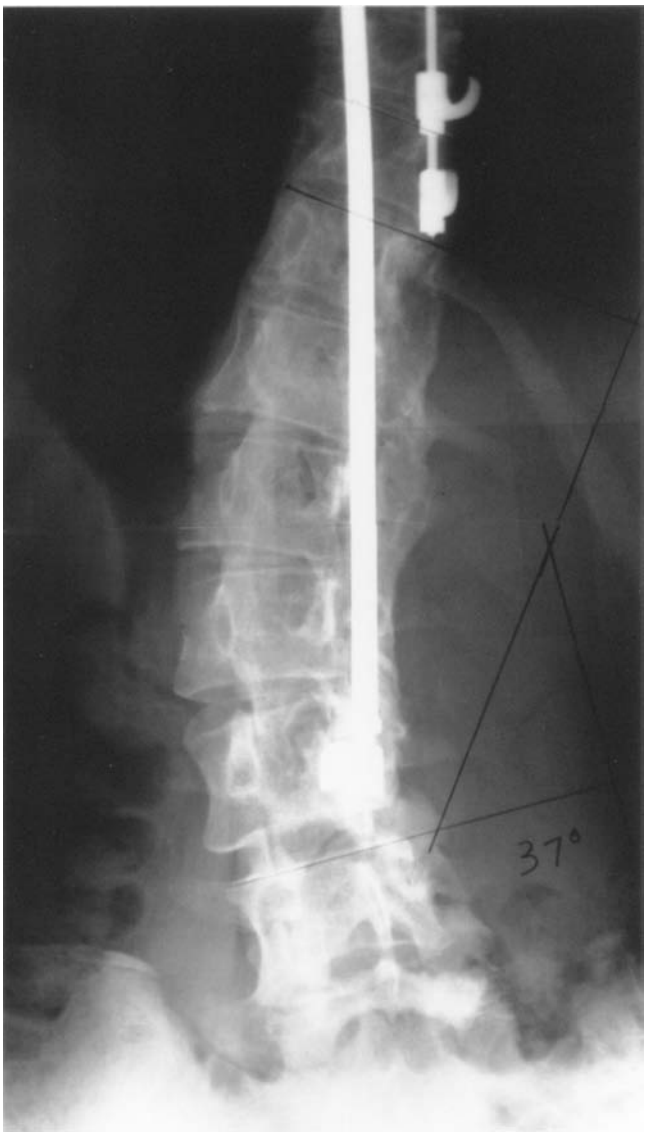

Figure 7.5 Harrington rod instrumentation. X-ray of the lumbar spine in a 31-year-old woman with thoracolumbar scoliosis corrected with spinal instrumentation. There is rotation of the vertebrae into the curve (toward the rod), and extensive bone grafting is evident adjacent to the rod. Two lumbar interspaces are not involved in the fusion, L4–L5 and L5–S1. (From Crosby, E. T. Musculoskeletal disorders. In Chestnut, D. H. (ed.), *Obstetric Anesthesia: Principles and Practice*, 3rd edn. Philadelphia, PA: Elsevier Mosby, 2004, p. 861.)

exceeds 25%, and children with congenital heart disease have an increased incidence of scoliosis.[35] However, most patients with AIS do not have congenitally abnormal hearts. The cardiovascular abnormality that is most commonly associated with scoliosis results from the restrictive pulmonary defect. The consequences of impaired lung development and alveolar hypoxemia are increased pulmonary vascular resistance, pulmonary hypertension and right ventricular (RV) hypertrophy. Permanent changes of the pulmonary vasculature are common with curvatures > 65°.

A brief discussion of the parturient with pulmonary hypertension follows; the evaluation and care of patients with pulmonary hypertension is discussed in detail in Chapters 1 and 3. Pulmonary

hypertension complicating respiratory disease is generally defined as a resting mean pulmonary artery pressure (PAP) exceeding 20 mmHg.[36] This differs from the definition of primary pulmonary hypertension, which is a pressure of 25 mmHg at rest or 30 mmHg during exercise. Pulmonary hypertension at rest or with exercise occurs in many patients with a moderately advanced deformity long before the onset of detectable right heart failure.[7] Pulmonary hypertension is mainly attributable to increases in pulmonary vascular resistance (PVR) resulting from chronic alveolar hypoxia ($PaO_2 < 60$ mmHg), hypoxic pulmonary vasoconstriction, and anatomic vascular alteration. Fixed pulmonary hypertension, unresponsive to supplemental oxygen (O_2) therapy, carries a grave maternal prognosis during pregnancy and is an indication to recommend termination of pregnancy.[37,38,39]

Patients with pulmonary hypertension have a limited ability to increase cardiac output (CO) with activity.[40] Because of the limited CO, tachydysrhythmias are not well tolerated and may produce marked systemic hypotension. If the RV fails in the presence of pulmonary hypertension, left ventricular (LV) filling decreases and low-output failure and sudden death may occur. Death may be caused by sudden changes in venous return to the right ventricle, with acute LV failure, ischemia, and dysrhythmias. Hypoxia, due to the increased O_2 consumption associated with labor as well as the underlying pulmonary dysfunction, further compromises cardiovascular function by increasing PVR and RV afterload, and decreasing CO.[41] Tiny pulmonary emboli may be fatal in established pulmonary hypertension because cardiac reserve may be so marginal that even a small decrease in vascular compliance may fatally compromise ventricular function.

Scoliosis associated with neuromuscular disease: Cardiopulmonary manifestations

The pathophysiologic sequelae of scoliosis developing consequent to a primary neurologic or myopathic disorder differ from those of idiopathic scoliosis. Abnormal respiratory function results not only because of the skeletal deformity of scoliosis but also because of abnormalities in the central control of respiration and in supraspinal innervation of muscles. Abnormal respiratory function results also from loss of muscle function due to lesions of the motor neurons and peripheral nerves or as a result of myopathy. Further compromise may result from impairment of the airway defense mechanisms caused by loss of control of the pharynx and larynx, by ineffective cough mechanisms, and by infrequent or reduced large breaths. Recurrent aspiration pneumonitis results from these compromised airway-protective reflexes. The prognosis for the patient with scoliosis caused by neuromuscular disease is determined predominantly by progression of the primary disorder and is worse than that for idiopathic scoliosis.

The neuromuscular disorders usually involve both inspiratory and expiratory muscles, resulting in moderate to severe decreases in inspiratory capacity and expiratory reserve volume. Until the diseases are well advanced or until a significant degree of thoracic scoliosis is superimposed, FRC remains normal. Hypoventilation is a prominent feature of the neuromuscular disorders associated with scoliosis. Diaphragmatic weakness or paralysis attributable to the underlying disorder can further compromise VC. If ribcage expansion is limited by neuromuscular involvement, respiratory function is severely compromised and a restrictive pattern of lung disease develops. With advancing gestation, encroachment of the expanding uterus further compromises lung function and respiratory insufficiency results. Hypoxemia may be present for prolonged periods before the onset of hypercapnia. Pulmonary vasoconstriction, hypertension, and RV failure occur owing to the same etiologic considerations as for idiopathic scoliosis. A primary myocardial impairment may also be superimposed on the acquired cardiovascular derangements in conditions such as muscular dystrophy and Marfan disease.[42]

An example of a neuromuscular disorder is spinal muscular atrophy (SMA), a genetic syndrome characterized by progressive degeneration of spinal anterior horn cells (see Chapter 10). After Duchene dystrophy, SMA is the most common serious neuromuscular disease of childhood, and after cystic fibrosis, it is the second most common autosomal recessive disorder (estimated incidence 1 in 10 000).[43] The clinical spectrum is wide and ranges from severe weakness and death during infancy to minimal weakness with little impact on life expectancy. Marked scoliosis is a common manifestation of more severe expressions of SMA, especially in patients with onset early in childhood. Historically, these women would have been discouraged from reproducing, but with advances in medical care, longer-term survival is expected and many of these women ultimately choose to have a partner and have children. Case reports and case series detailing the reproductive experiences of women with SMA and the care provided to them are increasing.[44]

Interaction of pregnancy with scoliosis

Impact of pregnancy on the spinal deformity

Pregnancy may exacerbate both the severity of spinal curvature and the cardiorespiratory abnormalities in patients with uncorrected scoliosis. The factors that predict curve progression are the same in parturients as they are in nonpregnant women. Thus, a young, skeletally immature woman with scoliosis would be at particular risk for curve progression during pregnancy. Curves that are $<25^\circ$ or curves that have been stable before the pregnancy do not, as a rule, progress during pregnancy.[45,46,47] More severe curves and those that have not yet stabilized may progress, although curve progression during pregnancy is uncommon.[14,15] There is no evidence of curve progression in women treated with bracing or surgery as adolescents, who subsequently become pregnant.[14,15] In two studies,[14,15] women were followed for an average of 22 and 17 years. Maternal morbidity and mortality have been linked to the severity of the curve, but the true correlation appears to be with the degree of functional impairment present before pregnancy.[48] Patients with severe curves (Cobb angle $\geq 90^\circ$) but good cardiopulmonary function tolerate pregnancy well.[49] The incidence of gestational back pain is higher than expected in patients with uncorrected scoliosis, but not in those who have undergone spinal fusion.[50]

Effect of pregnancy on the cardiopulmonary pathophysiology of scoliosis

When evaluating the parturient with significant cardiopulmonary disease, an attempt has to be made to distinguish the signs and symptoms that are consistent with normal pregnancy and advancing gestation from those that may herald deterioration in a chronic maternal condition. For example, although most parturients complain of dyspnea by the middle of the third trimester, exercise testing shows no deterioration in exercise response during moderate activity. A pathologic deterioration in respiratory function is associated with a significant decrease in exercise tolerance. Two features help distinguish physiologic from pathologic dyspnea.[51,52] Physiologic dyspnea tends to begin earlier in pregnancy and often reaches a plateau or improves as term approaches. It is rarely extreme, and patients can usually maintain daily activities. The dyspnea of cardiopulmonary decompensation is progressive, becoming more severe as gestation advances and physiologic demands are increasing. If dyspnea is extreme, has a limiting impact on normal activity, occurs at rest or with minimal exertion, or is associated with a cough, maternal cardiorespiratory decompensation should be ruled out.[51] Dyspnea that is acute in onset or progressive and intractable, especially if coupled with other signs and symptoms (orthopnea, paroxysmal nocturnal dyspnea), is more likely to represent cardiopulmonary disease.

The thoracic cage expands in circumference during normal pregnancy as a result of increases in both anteroposterior and transverse diameters. Little potential exists for further thoracic cage expansion during inspiration. Inspired volumes in the term pregnant woman are largely attributable to diaphragmatic excursion. If the chest cage is fixed by scoliosis, the diaphragm is entirely responsible for all increments in minute ventilation (MV). As the enlarging uterus enters the abdominal cavity in midgestation, diaphragmatic activity is constrained. Functional residual capacity decreases to 70% (supine) to 80% (upright) of nonpregnant values by term gestation. Closing capacity (CC) is also reduced. Even greater than anticipated decreases in FRC and CC may be seen in patients with scoliosis, resulting in V/Q mismatch and reduced arterial O_2 content.

Minute ventilation increases by 40 to 50% during pregnancy and the increase is primarily a result of increased tidal volume (VT), with respiratory rate relatively unchanged. In the scoliotic patient with restrictive lung disease, such rises in VT may not be possible, and the increased MV is achieved via increased respiratory rate. Increased respiratory rate increases both wasted ventilation and the work of breathing; respiratory failure may result. The greater demands on the pulmonary system peak by mid-third trimester. However, because the uterus continues to grow through the last trimester, it may encroach further on the noncompliant thorax and cause deterioration despite the fact that respiratory demand has stabilized. The onset of new respiratory symptoms or the exacerbation of preexistent symptoms during the antepartum period is associated with an increased rate of maternal morbidity as well as a requirement for assisted ventilation around the time of delivery.[53] During labor, MV of the unmedicated parturient increases by a further 75 to 150% in the first stage and by 150 to 300% in the second stage. These levels may be either unattainable or unsustainable by the scoliotic parturient with restrictive lung disease, and respiratory insufficiency or failure may result.

Table 7.2 Risk factors for ventilatory failure in parturients with neuromuscular scoliosis

Elevated $PaCO_2$
Bilateral diaphragmatic impairment
Extensive intercostal muscle weakness
Vital capacity <1.0 liter
Cobb angle >100°

In parturients with neuromuscular scoliosis, decreased lung volumes with advancing pregnancy result in increased V/Q mismatching, decreased arterial O_2 content, and carbon dioxide retention. These effects may be especially marked during sleep because of a further reduction in lung volumes due to loss of muscle tone during sleep and enhanced cephalad shift of the diaphragm during supine positioning. The upper airway resistance rises during pregnancy because of mucosal hyperemia, increasing secretions, and occasional development of nasal polyps. These changes predispose the patient to snoring and obstructive sleep apnea.[54] Weakness of the muscles that stabilize the upper airway is common in diffuse muscle disorders: the weakness may increase the incidence, severity, and maternal–fetal implications of the sleep apnea that develops. All of these factors increase alveolar hypoxia and worsen pulmonary hypertension.[36] A stage of dyspnea on exertion as a prelude to more severe incapacity is seen only rarely in neuromuscular scoliosis. This is perhaps because neuromuscular dysfunction has possibly long since rendered such exertions untenable. Risk factors for ventilatory failure during pregnancy have been identified (see Table 7.2).[55] The use of noninvasive (negative pressure) ventilation to reduce dyspnea and improve respiratory function has been reported.[43]

Cardiac output increases about 40% by the end of the first trimester and is 50% above nonpregnant levels by the third trimester; both heart rate and stroke volume increase to augment CO. In scoliotic parturients who already have increased PVR, it may not be possible to achieve this increase in CO without further increments in vascular pressures, increasing RV afterload. This may place an intolerable load on the RV, precipitating right heart failure with low CO leading to poor myocardial perfusion and refractory failure. Death at the time of delivery or in the early postpartum period is common in parturients with pulmonary hypertension.[38,39,41]

Outcome of pregnancy in scoliotic parturients

Isolated cases of maternal death during pregnancy and the postpartum period have been reported with scoliosis, although pregnancy is usually well tolerated with few medical or obstetric

complications.[13,14] In the Reports on Confidential Enquiries into Maternal Deaths in the United Kingdom covering the years 1985–1987 and 1988–1990, there were two cases of maternal mortality associated with scoliosis, one in each report.[56,57] Both patients were admitted to hospital with deteriorating respiratory status, underwent C/S, and died postoperatively. One death was attributed to adult respiratory distress syndrome and multiorgan failure, the other to air embolism. These deaths, viewed in light of the comments regarding the usually benign course of pregnancy in the scoliotic parturient, probably reflect the lack of homogeneity in the population of parturients with scoliosis. There have been no similar cases detailed in subsequent reports.

The reproductive experiences of women with scoliosis depend not only on the severity of the curve and the resulting cardiopulmonary sequelae but also on the presence of underlying neuromuscular disorders. Kafer suggested that complications are more likely to occur in the older parturient (>35 years) with severe scoliosis, or in a parturient with scoliosis associated with an underlying neuromuscular disease.[3] Also at risk are primiparas who develop fatigue during long labors. Premature labor is reported by some to occur more commonly in scoliotic parturients and to be independent of the severity of the curve.[12,50,53] However, this observation was not found in two of the largest series of parturients with treated idiopathic scoliosis.[13,14]

The incidence of low-birth-weight infants and congenital anomalies is not increased in women with moderate uncorrected or corrected curves, compared with population averages.[12,13,14] The likelihood of intrauterine fetal compromise rises with the frequency and severity of maternal hypoxic episodes.[55] Malposition at delivery is not common; in patients without cephalopelvic disproportion, vaginal delivery occurs uneventfully at a rate similar to controls. When scoliosis or other underlying disease distorts pelvic anatomy, operative or instrumented deliveries, perineal tears, and uterine prolapse occur with greater frequency, leading to a higher rate of fetal and maternal morbidity.

In the second stage of labor, the diaphragm not only acts as a respiratory muscle but also has a nonrespiratory function. With expulsive efforts, maximal isometric diaphragmatic contractions are often sustained for 10 to 20 seconds. Diaphragmatic fatigue has been demonstrated in normal laboring women.[53] In one report the incidence of acute respiratory failure during delivery was virtually zero in healthy parturients, but in the woman whose diaphragm is weak due to neuromuscular disease, the potential for respiratory difficulties increased.[58] Expulsive forces are also decreased and may lead to a prolonged second stage or even failure of a trial of labor. Cesarean delivery is necessary in a significant proportion of scoliotic parturients. The incidence is likely to be related to the degree of skeletal deformity, resulting maternal compromise, and cephalopelvic disproportion. In patients with severe curves, the rates for C/S range up to 52%.[4,59,60] Cesarean delivery may be technically more difficult in patients with severe curves, especially those with lumbar spinal involvement. This difficulty is due to the acute anteflexion of the uterus in the small abdominal cavity resulting from the approximation of the xiphisternum and the symphysis pubis. The lower uterine segment may be inaccessible, making classic C/S necessary.[60] Kopenhager, however, reporting on 25 C/S in women with severe kyphoscoliosis, noted that classic C/S was required in only one.[4]

Patients with corrected scoliosis tolerate pregnancy, labor, and delivery well, although some studies have demonstrated an increased incidence of operative delivery compared with that in normal parturients.[61] In one study, the rate of vacuum extraction was higher in surgically treated women (16%) than it was in either brace-treated (8%) or a control cohort (5%).[13] Others have noted no increased requirement for operative delivery in patients with corrected scoliosis. Orvomaa reported that rates of complications of either pregnancy or labor were similar to national statistics and although there was an increased requirement for C/S, the indications for surgery were not typically scoliosis-related.[14] In a report of 355 patients with scoliosis and prior posterior fusion, C/S was necessary in only 2.5% of deliveries.[47] In another review of 17 women with kyphoscoliosis who had 27 pregnancies: nine had idiopathic scoliosis, and posttraumatic scoliosis was the largest single second etiologic factor.[15] Again, the experience was similar to that seen in the nonaffected population.

Management issues in the scoliotic parturient

Antepartum assessment and medical management

Prepregnancy planning in women with scoliosis serves two purposes. It allows for counseling regarding the risk of inheritable disease in offspring when there is a significant genetic component, and it allows for evaluation of maternal risk in carrying a gestation to term. The majority of patients with scoliosis have mild to moderate idiopathic curves, and the expectation is that they will tolerate pregnancy, labor, and delivery with an incidence of complications comparable to that in the normal population. Maternal morbidity is predominantly due to cardiopulmonary failure and is related to the site (thoracic) of the curvature and degree of cardiopulmonary compromise before pregnancy. Morbidity and mortality increase if the vital capacity is <1 to 1.25 liters, if $PaCO_2$ is elevated, or if pulmonary hypertension with ventricular compromise is present.[55,62,63,64,65] These are considered indications for recommending avoidance of, or termination of, the pregnancy. Pregnancy is well tolerated if antenatal lung volumes exceed 50% of those predicted.[45,48] Scoliosis secondary to a primary neuromuscular disorder may be associated with higher gestational morbidity than idiopathic scoliosis.[55] Young women with curves that are >25° and those that involve a double curve and are not yet stable should be advised that there is some risk of progression of the curve from pregnancy. Conversely, there is little risk of progression if the curve is <20° or has been stable, and no risk if the curve has been surgically stabilized.[13,14]

Antepartum maternal assessment focuses on maternal cardiorespiratory status with attention to the history and current status; presence of coexistent disease; and type, status, and patient prognosis of associated neuromuscular disorders. If respiratory compromise is evident, a formal respiratory evaluation is carried out. An assessment is made of the respiratory reserve, including inspiratory and expiratory muscle function, and integrity of the airway-protective reflexes. Special attention is given to the

presence of dyspnea, tachypnea, and exercise tolerance; recent pulmonary function assessments are noted. Further evaluation is made with respect to the possible benefits of supplemental O_2 therapy, nocturnal continuous positive airway pressure (CPAP), or assisted (negative-pressure) ventilation. Patients with curves $>60^\circ$ or those with known cardiac disease require formal cardiologic evaluation to assess ventricular size and function as well as pulmonary vascular pressures.

If maternal cardiopulmonary status is so compromised that her survival is jeopardized by continuation of the pregnancy, a recommendation to terminate the pregnancy may be made. Despite the risk, many will choose to continue with pregnancy. The value of a team approach to these high-risk patients cannot be overemphasized. The team includes medical, obstetric perinatology, neonatology, and anesthesiology consultants; the team can be complemented by nursing and social services personnel. The team meets, in whole and in part, at regular intervals to monitor both the condition of the mother and progress of the pregnancy. A plan is generated regarding the management of the pregnancy and delivery. The plan is relayed to the patient and is shared with the departments involved. Such an approach to management may reduce the incidence of morbidity and mortality even in very high-risk parturients.[62]

Patients with underlying neuromuscular disease or cardiopulmonary dysfunction related to scoliosis represent a particularly high-risk group for antepartum maternal decompensation. Admission to hospital for the last weeks of pregnancy enhances the likelihood that maternal decompensation will be recognized early and morbidity or mortality prevented. Oxygen therapy (2–4 l/min by nasal prongs) intermittently during the day and continuously overnight may improve maternal condition and reduce fetal risk. Both negative- and positive-pressure noninvasive ventilatory support for respiratory insufficiency during pregnancy in parturients with severe kyphoscoliosis has been reported.[66,67] The patient whose diagnostic images are profiled in Figures 7.2 and 7.6 underwent negative-pressure ventilation for several weeks before delivery, initially intermittently and nocturnally, then subsequently continuously. Chronic hypoxemia and polycythemia combined with the hypercoagulable state induced by pregnancy increase the risk for thromboembolic events.[39,63] Antiembolism stockings are recommended. Consideration should also be given to subcutaneous heparin therapy, with full anticoagulation being reserved for the patient with more severe disease. Heparin may be reversed at induction or with onset of labor to allow for neuraxial analgesia.

Obstetric management

In parturients with little or no cardiopulmonary compromise at the outset of pregnancy, the expectation is for an uneventful

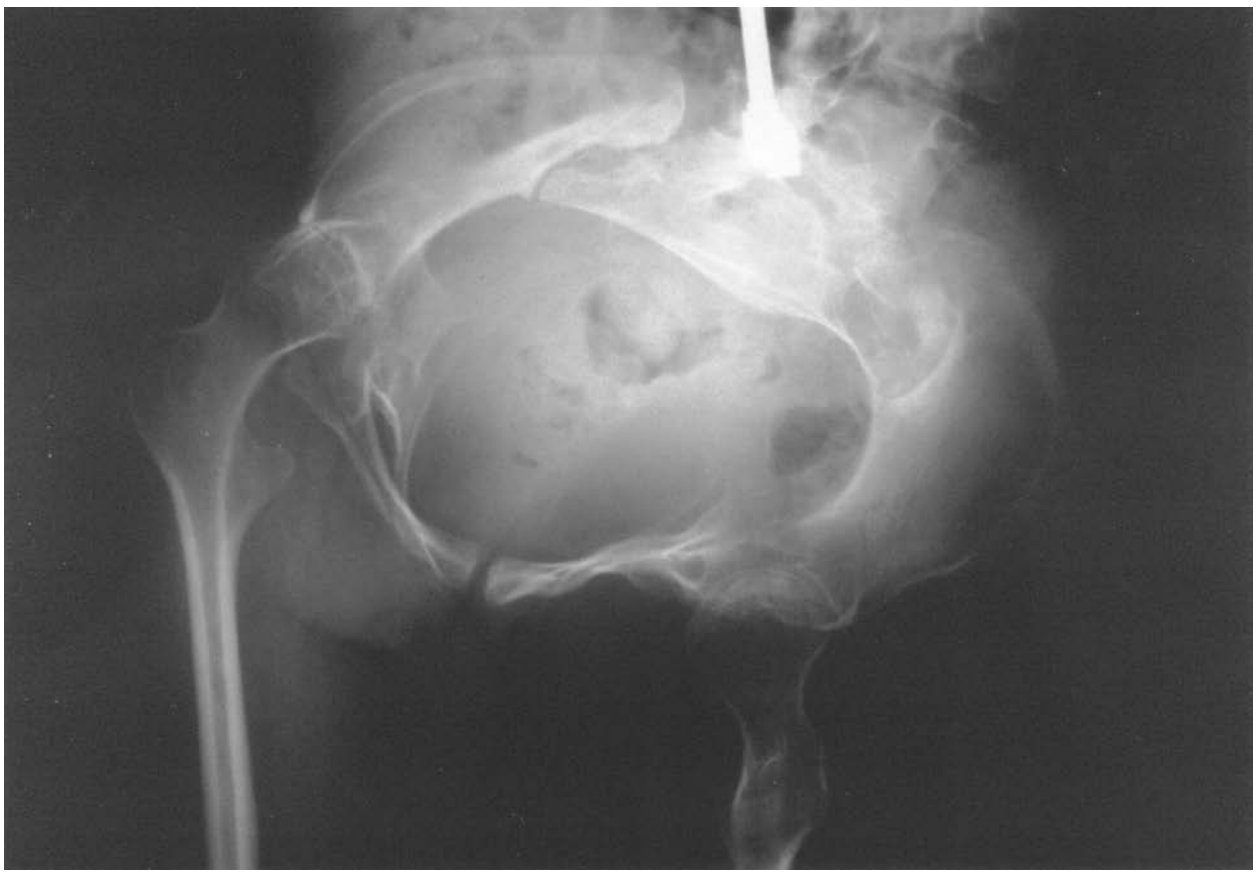

Figure 7.6 Pelvic x-ray study in a young woman with a progressive spinal muscular atrophy (Kugelberg-Welander syndrome) demonstrating an inadequate pelvic outlet. She delivered two children by C/S under GA after failed attempts to perform regional anesthesia. Her chest film is detailed in Figure 7.2.

pregnancy and delivery. As the pregnancy advances, the cardiopulmonary signs and symptoms of a normal course must be differentiated from true deterioration in function. The obstetrician or perinatologist is in the best position to monitor for untoward maternal responses to the advancing gestation by virtue of the frequency of contact with the woman. If there is concern that the maternal condition is deteriorating, a reevaluation by a medical consultant is in order to quantify the change and to initiate therapy. Although right-sided heart failure may mimic preeclampsia, peripheral edema being common in both, respiratory symptoms are usually profound in cor pulmonale and are uncommon in preeclampsia. Maternal decompensation early in the pregnancy confers an ominous prognosis. Decompensation in late pregnancy and during the early postpartum period is common in the patient with borderline cardiopulmonary function. Obstetric intervention before the completion of gestation is reserved for compelling maternal or fetal indications.

At term, if maternal cardiopulmonary function and pelvic size are adequate and the fetal condition is good, a trial of labor is permitted and should be successful. Cesarean delivery is reserved for obstetric indications. A higher incidence of operative delivery may occur in patients with spinal fusion for scoliosis; but this has not been a consistently reported finding.[12,13,14,56,62,65]

In women without major lumbosacral deformity, there is little alteration of the pelvic cavity, and malpresentation is no more frequent.[4,12] In patients in whom a lumbar spinal deformity is prominent, however, malpresentation is common.[60,68] Pelvic abnormalities are also more common when scoliosis is associated with neuromuscular disorders, which predisposes the fetus to malpresentation (see Figure 7.6).[55] Uterine function is typically normal in scoliosis; labor is not prolonged and spontaneous vaginal delivery is to be anticipated. In patients with severe disease, those with scoliosis resulting from neuromuscular disease and especially in those with gestational decompensation, C/S may be indicated because of maternal compromise. Patients with significant pulmonary hypertension should avoid bearing down, and a forceps-assisted vaginal extraction facilitates delivery in these patients. Oxytocin is a systemic vasodilator, and bolus doses should be avoided in parturients with pulmonary hypertension.[39]

Anesthetic management

Antepartum assessment

Patients who require antepartum anesthetic consultation include those with pulmonary hypertension, thoracolumbar scoliosis with a Cobb angle $>30^{\circ}$, and spinal instrumentation and fusion for scoliosis. Initial anesthesiology contact should occur early in gestation, not later than the second trimester. The more severe the maternal condition, the earlier first contact is advised. Ongoing evaluation is carried out via team conferences and a plan for anesthetic management is formulated well before delivery. The plan is conveyed to the patient and other team members.

The underlying etiology of the scoliosis as well as severity and stability of the curve should be elucidated. In patients with scoliosis resulting from neuromuscular disorders, anesthetic considerations specific to those disorders should be reviewed.[69] Radiographic studies done before pregnancy and operative notes related to surgical procedures on the spine should be assessed in any patient with a significant scoliosis or previous major spinal surgery before consideration is given to regional anesthesia. Reviewing films taken in the past, even before pregnancy, is usually sufficient to determine not only the underlying anatomy but also the residua of previous surgical interventions. If further diagnostic imaging is required, it should be deferred until there is little threat to the fetus (late second or third trimester). The spine should be examined and note made of the surface landmarks and the interspaces least involved in the deformity.

Anesthetic care of parturients with scoliosis complicated by pulmonary hypertension

The care of parturients with pulmonary hypertension is discussed in detail in Chapters 1 and 3 and will only be detailed briefly here. The goals in the anesthetic management of parturients with pulmonary hypertension include (1) avoidance of pain, hypertension, hypoxemia, hypercarbia, and acidosis, because these increase PVR; (2) avoidance of myocardial depression because CO will be further decreased; (3) maintenance of intravascular volume and preload; and (4) maintenance of systemic vascular resistance (SVR) so as to ensure myocardial perfusion and prevent right-to-left shunting. The use of regional block in parturients with pulmonary hypertension has been discouraged, historically.[70] However, recent reports suggest that regional anesthesia may be provided to these patients with relative safety, although this may depend on the degree of pulmonary hypertension.[62] Mortality, though considerable, seems dictated primarily by maternal condition at presentation and the intensity (major vs. minor) of the surgical intervention.[71] The concerns regarding the use of regional anesthesia include reducing venous return with sympatholytic vasodilatation as well as the possibility of creating or augmenting a right-to-left shunt and reducing myocardial perfusion by reducing SVR. Systemic hypotension resulting from regional block may also lead to RV ischemia and profound decreases in CO.

Invasive cardiac monitoring is recommended for those patients with significant cardiopulmonary dysfunction. A radial arterial line allows for continuous assessment of maternal blood pressure (BP) and serial arterial blood gases. Central venous pressure monitoring is also helpful in parturients with RV dysfunction. Insertion of the central line through the antecubital fossa veins prevents maternal distress resulting from the Trendelenburg position for insertion through the vessels in the neck, particularly in those patients who are already experiencing symptomatic cardiopulmonary decompensation.

Analgesia for labor

Modes of analgesia and anesthesia for labor and delivery can be discussed at the antepartum consultation. Patients with uncorrected thoracolumbar scoliosis may be offered lumbar epidural anesthesia (LEA) for labor and delivery, even if the deformity is severe. Placement of an epidural catheter is technically more

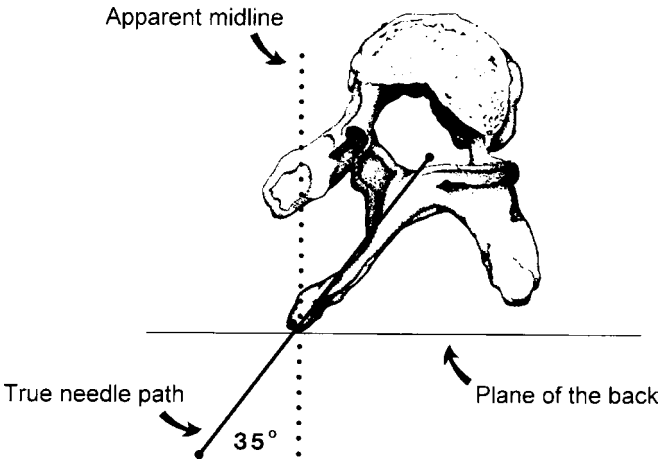

Figure 7.7 Vertebral displacement and rotation in moderate to severe scoliosis. The vertebral body deviates from the midline and undergoes rotation with the spinous process remaining closer to the true midline (defined as a line drawn from C7 to the sacrum). The interlaminar space is deviated toward the curve convexity. A needle entering the palpated interspinous gap must be directed toward the convexity of the curve to reach the interlaminar gap. Tracking the interspinous ligament can be used to determine the angle required; the angle is dependent on the magnitude of the curve.

demanding than usual and an increased incidence of complications should be anticipated. The midline of the epidural space is deviated toward the convexity of the curve, relative to the spinous process palpable at the skin level (see Figure 7.7).[21] The degree of lateral deviation is determined by the severity of the deformity. The needle should enter the selected interspace and be directed toward the convexity of the curve. The experienced clinician can track the resistance of both the interspinous ligament and the ligamentum flavum to maintain a true course into the epidural space. Structural curves of 30° or less and minor functional curves, such as those commonly seen in the term pregnant female, rarely result in much rotatory deviation of the vertebrae. Little accommodation in technique is required for successful needle or catheter placement.

Major spinal surgery in the past is believed by some to represent a relative contraindication to regional anesthesia. This opinion is not shared by me. Regional anesthesia and analgesia may be offered to patients who have experienced previous spinal instrumentations. The incidence of successful block is reduced and complications are more frequent, especially in patients who have had extensive surgeries involving the lumbar spine.[61,65,68,72,73] Complications include unsuccessful insertions, multiple attempts before successful insertion, false loss of resistance, dural puncture, failed block, or inadequate analgesia. Problems are more frequent in patients with fusions extending to the lower lumbar and lumbosacral interspaces than in those with fusions ending in the upper lumbar spine.[73] When discussing regional anesthesia with parturients who have previously undergone extensive spinal surgery, consideration should be given to the following.

1. Twenty percent of patients' spines are fused to L4 and L5 levels, leaving few lumbar interspaces uninvolved.[61,74]
2. Reliable surface landmarks are absent following surgery.
3. Degenerative changes occur in the spine below the area of fusion at a rate greater than usual, and these changes may increase the likelihood of technical difficulties entering the space or achieving a block.[75]
4. Insertion of an epidural needle by either the midline or paramedian approach in the fused area may not be possible because of the presence of instrumentation, scar tissue, and bone graft material.[72]
5. A false loss of resistance is common.
6. The ligamentum flavum may be injured during surgery, resulting in adhesions in the epidural space or obliteration of the epidural space, which may interfere with spread of local anesthetic (LA) injected into the epidural space.[76]
7. Obliteration of the epidural space may make accidental dural puncture inevitable in some patients.
8. It may not be possible to perform an epidural blood patch if a significant postdural puncture headache results.
9. Persistent back pain is common in patients with surgically corrected scoliosis (correlates with increasing time since the surgery and extent of fusion).[28,75]
10. Patients often manifest a high degree of anxiety about their backs and may be reluctant to have a regional block.

Once the epidural catheter is sited and its position verified, it may be activated with a solution of LA alone or with a LA-opioid mixture. In most parturients, and in particular those with significant cardiovascular compromise, a dilute LA-opioid mixture (bupivacaine 0.0625% – 0.1% with 2–4 μg/ml fentanyl at infusion rates of 8–15 ml/h) is more likely to provide excellent first-stage and good second-stage analgesia with fewer hemodynamic consequences compared with more concentrated LA solutions.[77]

Combined spinal–epidural analgesia is also an option in patients in whom the spinal spaces can be reached. The efficacy and complication profiles of the combined technique are similar to those of epidural analgesia.[78] Intrathecal opioids represent another option for labor analgesia. Although some reports suggest that there is less hemodynamic compromise than with LAs,[79,80,81,82,83] others state that the incidence and magnitude of hypotension is similar.[84] The use of intrathecal opioids for labor analgesia has been linked with fetal heart-rate abnormalities, although it is uncertain whether these occur more commonly than would be observed after epidural analgesia.[85,86,87] Continuous subarachnoid infusions of sufentanil or meperidine for effective labor analgesia have been described in both normal populations and in parturients with severe cardiac disease.[88,89,90] In the event that the opioid alone provides inadequate pain relief (i.e. perineal pain during second stage), small, hemodynamically innocuous doses of dilute LA solutions are usually adequate supplements.[88]

Labor analgesia in parturients with cardiopulmonary compromise

The utilization of small, incremental doses of dilute LA (bupivacaine 0.0625–0.1%, ropivacaine 0.08–0.125%) to initiate epidural blockade followed by a continuous infusion, should be well tolerated by most parturients.[62] The introduction of lipid-soluble

opioids (fentanyl 2–4 μg/ml) into the infusing solution reduces both the mass of LA required and the potential for significant cardiac decompensation with the initiation of regional analgesia. It is a prudent strategy to enhance the safety of regional anesthesia in this subpopulation and is highly recommended. Intrathecal administration of lipid-soluble opioids may also be an acceptable strategy to provide labor analgesia in these parturients, although hypotension may result from the administration of intrathecal sufentanil alone.[84] In patients in whom the lumbar spinal spaces cannot be safely reached, consideration may be given to the performance of a caudal block.

Anesthesia for operative delivery in parturients with scoliosis

Cesarean delivery may be indicated for maternal or fetal welfare or for obstetric reasons. Parturients with severe scoliosis often are small and frail. During surgery, the rib hump and bony prominences should be padded, with care taken to minimize heat loss. The patient's small size may occasionally necessitate pediatric-sized equipment, such as BP cuffs. Either general or regional anesthesia may be provided and there is no evidence that would support a specific choice in this patient population. If regional anesthesia is chosen, a slow and incremental extension of an epidural or a subarachnoid block provides ideal conditions for operative delivery and postoperative analgesia. Because LA dose requirements are variable, an epidural or a subarachnoid catheter is preferable to a single-shot subarachnoid injection. Particular attention should be paid to the dose of LA, because the patient's small size renders usual volumes toxic. In patients with severe curves, there is speculation that subarachnoid hyperbaric LA solution may pool in dependent portions of the spine, resulting in an inadequate block.[91] Supplementing the block with isobaric formulations of LA may improve the quality of the block; supplementation is facilitated with an indwelling subarachnoid catheter.

Multiple reports exist about LEA in parturients with severe scoliosis, including those with cardiopulmonary compromise and corrective instrumentation. Performance of regional block in these patients is technically demanding and may be complicated by failed or inadequate block. Block quality may be enhanced by supplemental epidural injection of chloroprocaine when dose limits of the other agents have been reached, or by subarachnoid injection of small doses of LA.[92] Reports have been published about extensive spinal blocks associated with profound hemodynamic instability when full-dose subarachnoid injection is made in the setting of preexistent, albeit inadequate, epidural blockade in parturients.[93,94,95,96] If time permits, allowing the epidural block to regress before performing spinal block is recommended.[97] Alternatively, reducing the dose of LA agent injected into the subarachnoid space is recommended if partial epidural block is present.[96]

The rate of mortality related to C/S in patients with pulmonary hypertension is considerable.[38,39,62,63,71] The high mortality rate is probably due in part to the presurgical status of the mother and reflects her poor condition. Prognosis is related to the preoperative maternal condition, with survivors demonstrating good RV function. There is evidence that LEA is as safe as general anesthesia (GA) in parturients with pulmonary hypertension. Both combined spinal–epidural anesthesia and continuous spinal anesthesia have also been reported with survival.[98,99] If regional anesthesia is used, a technique that permits cautious and incremental titration to achieve the required level of block is advocated.

General anesthesia may be indicated because of maternal preference, or maternal cardiopulmonary decompensation, or because of technical difficulties related to regional block. A thorough evaluation of the maternal airway is indicated, because a number of conditions associated with scoliosis, including severe scoliosis itself, are associated with difficult laryngoscopy and intubation. Many patients with scoliosis resulting from neuromuscular diseases have preexisting airway obstruction and may have sleep apnea. Because GA also causes relaxation of pharyngolaryngeal elements, patients may be at particular risk for airway complications postoperatively.[100] Postoperatively, elements of laryngeal incompetence and impaired swallowing may further decrease the integrity of the airway defense mechanisms.

In normal patients, the FRC falls at induction of anesthesia, which is attributable to cephalad shift of the diaphragm, ribcage dysfunction or instability, and increased intrathoracic blood volume. Abdominal surgery produces persistent postoperative decreases in FRC that are progressive, becoming evident hours after the end of surgery.[101,102] The decreases in FRC are related to diaphragmatic dysfunction and may persist for up to one week. Atelectasis and V/Q abnormalities, which impair gas exchange and result in hypoxemia in normal subjects, may occur. In scoliotic parturients with underlying pulmonary pathology, these effects are augmented and may result in significant postoperative morbidity. Other causes of postoperative hypoxemia that are of particular importance to patients with scoliosis are included in Table 7.3.

Anesthesia, tracheal intubation, and surgery result in mucociliary dysfunction and abnormal or retrograde mucous flow.[103] Reduced competence of the larynx increases the potential for postextubation aspiration in patients already at risk because of both the pregnancy and underlying airway disorders. Coughing and bucking at the end of surgery may transiently and significantly reduce FRC, resulting in further V/Q mismatch and hypoxemia.[104] Tracheal extubation after C/S in the parturient with gestational hypertension may result in significant increases in both systemic arterial and pulmonary artery pressures.[105] These

Table 7.3 Factors contributing to postoperative hypoxemia in scoliotic parturients

Increased V/Q mismatch
Increased alveolar-to-arterial O_2 gradient
Inhibition of hypoxic pulmonary vasoconstriction
Decreased CO
Underlying preexistent pulmonary disease
Restriction of chest-wall movement

pressure rises take on added significance in the setting of preexisting pulmonary hypertension. Criteria for postoperative extubation must include assessment of preoperative respiratory function. An assessment of respiratory muscle strength and ability to support the airway should be made in all patients, but it is particularly important in patients with preexisting compromise. Potential hazards of GA in parturients with pulmonary hypertension include the increased pulmonary artery pressures during laryngoscopy and intubation; adverse effects of positive-pressure ventilation on venous return; and negative inotropism of some anesthetic agents. These adverse effects can be largely attenuated by an opioid-supplemented induction and maintenance technique.[64] An obvious potential exists for neonatal respiratory depression with this technique, but that is easily managed by the neonatologist. Nitrous oxide should be avoided because it increases PVR. The patient may require high-surveillance care for up to a week following delivery because major cardiopulmonary complications are common during this period.

Management of acute maternal cardiac decompensation

Most pregnancies in mothers with severe pulmonary hypertension do not reach term, but reports suggest that neonatal survival has improved recently.[38,39] Weiss reported neonatal survival ranging from 87–89% depending on the etiology of the hypertension, compared with maternal mortality rates ranging from 30–56%.[39] Parturients may present in right heart failure and cardiogenic shock during gestation; mortality attributable to such a presentation is unfortunately high and survival is not expected. Urgent C/S is likely necessary to achieve fetal and perhaps maternal salvage. The immediate goal of therapy in this setting should be to decrease PVR, reducing RV afterload leading to an increase in CO. This increased CO may improve systemic BP and reduce RV ischemia.[106] Afterload reduction may be achieved by pulmonary vasodilation. Although sodium nitroprusside has been used in this setting, nitroglycerin is also an effective pulmonary vasodilator with fewer effects on the systemic vasculature and on fetal and uterine activity.[63] Unfortunately, systemic vasodilators also reverse hypoxic pulmonary vasoconstriction, which may worsen pulmonary V/Q matching and decrease diastolic pressure, resulting in decreased myocardial perfusion.[107] Recently, the use of a selective pulmonary vasodilator such as intravenous epoprostenol or inhaled nitric oxide has been reported in decompensated parturients with resulting maternal survival.[108,109] Vasopressors directly increase arterial BP but increase afterload as well. Norepinephrine is recommended to increase right coronary artery perfusion pressure and RV function and it is more effective than phenylephrine.[107] Contractility enhancing agents such as phosphodiesterase inhibitors and calcium sensitizers may have a role in the management of these patients but there are no reports at this time regarding their use in this scenario. If the mother survives the acute event, it is advisable to maintain pharmacologic support to allow RV afterload and volumes to decrease. Mortality remains high in the month after delivery and is presumed to be due to thromboembolic events, increased pulmonary vascular reactivity and a mismatch between declining myocardial contractility and altered preload.[39]

Other disorders of the vertebral column

Lumbar disc prolapse

Back pain is a common complaint in the parturient.[110] Its occurrence during gestation seems most closely correlated with the presence of back symptoms in the prepregnant state. However, new onset back pain is also common during gestation; it is likely related to both changes induced by relaxin and estrogen and the biomechanical stresses imposed on the axial skeleton. Lumbosacral disc bulges and herniations commonly occur in women of childbearing ages, occurring in slightly more than half the women in this age group, whether pregnant or not.[111] Despite the prevalence of back symptoms during pregnancy and the common occurrence of disc prolapse in women of childbearing ages, prolapse is uncommon during pregnancy, estimated to occur in 1 in 10 000 pregnancies.[112] The relative rarity of symptomatic disc prolapse during pregnancy may be due to the reluctance of pregnant women to engage in strenuous physical activities which might predispose to prolapse. Three authors have reported a total of 12 women with disc prolapse during gestation who presented with significant neurological symptoms.[113,114,115] Magnetic resonance imaging was employed and typically revealed disc herniation with compression of neural elements. Most of the patients were treated conservatively at the outset but were subsequently subjected to surgery due to intractable pain or progression of neurological deficits. Regional anesthesia was employed for both the disc surgery as well as for the subsequent labor and delivery without apparent sequelae.

A conservative approach is warranted when disc prolapse occurs in pregnancy; surgical intervention is reserved for women with bowel or bladder dysfunction. In the absence of progressive or significant neurological compromise or intractable pain, management is expectant.[116] Pregnant women with radiculopathy but no sphincter dysfunction are managed in much the same way as those who do not have radiculopathy. Magnetic resonance imaging is considered to be the imaging modality of choice and is not contraindicated during pregnancy. In the event that surgery is indicated, regional anesthesia may be used. There is limited obstetrical experience managing labor and delivery in women with disc prolapse. As symptoms become more severe, it is likely that C/S will be used to decrease intrathecal pressures and the risk of symptom exacerbation during labor and delivery.[112] Regional anesthesia is appropriate for the provision of labor analgesia and surgical anesthesia.

Osteoporosis of pregnancy

Osteoporosis associated with pregnancy, although still uncommon, has been increasingly described in the recent literature.[117] There is clear evidence of decreased bone mineral density during pregnancy. Prolactin results in osteopenia and circulating levels are increased in pregnancy. There are also increased

requirements for calcium during gestation and lactation, and there may be failure of the maternal skeleton to retain calcium against these demands. Typically, the axial skeleton is most impacted with vertebral and sacral fractures and femoral neck fractures most commonly reported. The clinical presentation often includes pain and may also include radiculopathy symptoms although these are not typical.[118] Both obstetrical and anesthetic interventions will be determined after case-specific evaluations and no general recommendations are made.

Spondylolysis and spondylolisthesis

Spondylosis is a defect of the pars interarticularis of the vertebral element; the neural arch is uninvolved in this anomaly. It may occur as either a congenital or acquired condition. If there is forward translation of the involved vertebrae with respect to the adjacent vertebrae, the condition is termed spondylolisthesis. Both conditions seem to be more common in women and occur frequently in women of childbearing ages. Degenerative spondylolisthesis is most common at the L4–L5 level and in women.[119] Pregnancy does not appear to constitute a risk for increased low-back symptoms in women with spondylolysis or progression of spondylolisthesis.[120] However, women who have had children have a significantly higher incidence of degenerative spondylolisthesis in later years.[119] Pregnancy does not appear to complicate either spondylolysis or spondylolisthesis in the majority of patients. The obstetrical and anesthetic management of individual patients with concurrent pregnancy and spondylolysis or spondylolisthesis must be determined on a case-by-case basis.

Conclusions

It should be anticipated that most scoliotic patients will experience pregnancy, labor, and delivery with a similar incidence of complications as the general population. Within the population of scoliotic parturients, however, there is a subpopulation at high risk for morbidity and mortality. These patients include those with scoliosis resulting from neuromuscular disorders and those with severe restrictive pulmonary disease complicated by pulmonary hypertension. These patients are best served by a multidisciplinary team approach. Evidence exists that such an approach results in an improved outcome for both mother and child. Involvement of anesthesiologists in these multidisciplinary units is both medically advisable and personally rewarding. With respect to the obstetrical and anesthetic management of patients with less common and less extreme syndromes affecting the vertebral column, management is best determined after assessment of individual case characteristics.

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8 MISCELLANEOUS SKELETAL AND CONNECTIVE TISSUE DISORDERS IN PREGNANCY

Caroline Grange

Introduction

This chapter discusses a variety of miscellaneous conditions found during pregnancy, each with different degrees of rarity. It focuses on the pathophysiologic changes that occur with each disease in order to highlight the impact on both anesthetic and obstetric management. However, as some of the conditions described have a wide and varied organ involvement, firm management conclusions cannot be made. Each case should be assessed individually and the risk/benefit of any given anesthetic choice should be evaluated for each particular patient.

Gorlin syndrome (Gorlin-Golty syndrome or nevoid basal cell carcinoma syndrome)

Gorlin syndrome was first described in 1960.[1] The characteristic features are multiple basal cell nevi, odontogenic keratocysts of the mandible, and other congenital, mostly skeletal, abnormalities.[2] A variety of other neurological, genital, endocrine, and ophthalmic manifestations are also associated with this disease. A predisposition to tumor formation is well documented; those described include ovarian fibromas, central nervous system (CNS) tumors (mostly medulloblastomas), skin, and, occasionally, cardiac tumors.[3] Although this disorder has an autosomal dominant mode of inheritance, 50% arise from spontaneous mutations. The causative gene mutation is located on chromosome 9q22.3, which is normally required for the function of a transmembrane receptor involved in patterning and growth. This Gorlin mutation reduces its ability to act as a tumor suppressor gene resulting in the increased incidence of cancers. Males and females are equally affected and the disease prevalence is about 1 per 60 000.[4] The condition has a variable phenotypic expression with most cases reported in Caucasians. This may be due to the protective effect of melanotic pigmentation in black ethnic groups that prevents the formation of basal cell carcinomas.[5]

Southwick and Schwartz[6] followed a group of 36 patients with Gorlin syndrome, three of whom had severe bradycardic/hypotensive reactions to general anesthesia (GA). The authors postulated that the patients might have had an unusual response to thiopental. However, as there was minimal discussion of the patients' preoperative status and anesthetic details, there was little evidence to make this conclusion. There are no other similar reports in the literature.

There are two reports of pregnant patients with Gorlin syndrome associated with renin-secreting ovarian tumors.[7,8] The first patient[7] needed a laparotomy at 17 weeks' gestation, due to suspected malignant ovarian tumors. General anesthesia was induced with etomidate and succinylcholine and maintained with halothane, fentanyl, and pancuronium. The operation was uneventful except for hypertension, which occurred on handling the tumor. The patient made a good recovery but delivered prematurely at 27 weeks.

The second pregnant patient[8] had uncontrolled hypertension despite medical management and required a second trimester laparotomy for removal of a renin-secreting ovarian tumor. Surgery was performed successfully under combined epidural and general anesthesia. She had an uneventful delivery at term. Both patients had mandibular cysts but intubation was uneventful. The risks and benefits of either regional or GA will depend on individual features of the patient (see Table 8.1). However, if a renin-secreting tumor is suspected, it may be advantageous to use regional anesthesia to prevent hypertensive surges.

Noonan syndrome

Noonan syndrome was first described in 1963[9] and is a disorder characterized by abnormalities of the facial, cardiovascular, and skeletal systems.[10] Inheritance is usually autosomal dominant, although most cases are due to new mutations (1:8000 births). The chromosomal abnormality is a mutation in the PTPN11 gene on chromosome 12q24.1.[11] Males and females may exhibit Noonan syndrome, but males have cryptorchidism and hypoplastic testes (so are rarely fertile), whereas females are usually fertile, although their menarche is often delayed. Maternal transmission of the gene is reported to occur three times as frequently as paternal transmission.[12] The syndrome is similar to Turner syndrome with respect to short stature, characteristic facies (ptosis, downward slanting eyes, hypertelorism, hooded eyelids, broad flat nose, high arched palate, micrognathia, abnormal ears), shield-shaped chest deformity, and webbing (+/− fusion) of the neck. However, Noonan syndrome differs in that patients have a normal karyotype, a risk of mental retardation, coagulation defects, skeletal abnormalities, and associated heart lesions (mostly right sided rather than left, as in Turner syndrome).[13] The most frequently reported cardiac abnormality is pulmonary stenosis (usually with a dysplastic valve), although a diverse range of abnormalities have been described.[14,15]

Improving results from cardiac surgery in childhood mean that more women with complex Noonan syndrome are becoming pregnant. Parturients are at risk of operative delivery due to their contracted "male"-type pelvis and increased risk of cephalopelvic disproportion. These patients should be assessed early in the prenatal period to discuss anesthetic and obstetric

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Table 8.1 Clinical features of Gorlin syndrome

Organ	Disease process	Anesthetic implications
CNS	CNS tumors	Raised ICP
	Medulloblastomas (3–5%)	
	Meningioma (1%)	
	Congenital hydrocephalus	
	Mental retardation (mild)	Consent/ management issues
Skin	Basal cell carcinoma (50–97%)	Nil
	Palmar and/or plantar pits (90%)	
Skeletal		
Orofacial	Odontogenic keratocysts (75%)	Airway management issues
	Maxillary hypoplasia	
	Mandibular hyperplasia	
	Cleft lip/palate	
	Macrocephaly (40%)	
	Frontal bossing (25%)	
	Hypertelorism (5%)	
	High arched palate (40%)	
	Widened nasal bridge (60%)	
Spine	Scoliosis	Poor respiratory/ CV function
	Hemivertebrae	Difficulty with regional anesthesia
	Spina bifida occulta	
	Fusion defects	
Rib	Bifid/hypoplastic (38–60%)	Poor respiratory/ CV function
	Chest wall deformities	
Cardiac	Fibromas (3%)	Poor ventricular function
		Conduction defects
		Risk of endocarditis
Ovary/ uterus	Fibroma (15%)	Hypertensive responses
	(some renin-secreting)	

CNS = central nervous system; ICP = intracranial pressure; CV = cardiovascular

Table 8.2 Clinical features of Noonan syndrome

Organ	Disease process	Anesthetic implications
Airway	High arched palate	Possible difficult intubation
	Short webbed neck	
	Micrognathia	
Chest wall	Pectus deformity	Limited respiratory reserve
	"Shield-shaped" chest	
Spine	Kyphoscoliosis	Regional techniques difficult
	Lumbar lordosis	
	Narrow spinal canal	
	Short stature	
Cardiac	Congenital heart disease	Limited cardiac reserve
	Mostly right sided	Conduction defects
	PS/ASD (69%)	Risk of endocarditis
CNS	Mental retardation	Implication of consent and awake procedures
Hematological	Bleeding diatheses	Possible contraindication to regional techniques
	Deceased factors (e.g. XI, XII, VW)	
	Platelet dysfunction	Perioperative hemorrhage
	Thrombocytopenia	
Renal	Congenital abnormalities	Possible renal dysfunction
Dermis/ epidermis	Lymphedema	Difficult intravenous access
	Redundant skin	

PS = pulmonary stenosis; ASD = atrial septal defect; CNS = central nervous system; VW = Von Willibrand disease

management issues. The preoperative assessment should be aimed, in particular, at cardiac function (electrocardiogram [EKG] and echocardiogram if symptomatic or physical signs present), respiratory function (arterial blood gases, lung function tests as necessary), airway (possibility of awake intubation discussed), and renal function (electrolytes and creatinine) (see Table 8.2). Possible contraindications to regional anesthesia, such as spinal abnormalities or evidence of bleeding diathesis[16] (history of easy bruising, prolonged bleeding after tooth extraction), should also be sought. Factor deficiencies occurred in 50% of patients reported by Sharland,[14] the commonest being a reduction in factor XI, although there are reports of a wide range of deficiencies in platelets and other coagulation factors. Lee[17] reported spinal abnormalities in 30% of cases with Noonan syndrome, including significant scoliosis and lordosis. Although odontoid dysplasia with atlantoaxial instability frequently occurs with syndromes affecting the axial skeleton, making intubation a concern, there are no reports of cervical instability associated with Noonan syndrome.[18] There are few reports of anesthesia in patients with Noonan syndrome[19,20] and only six cases in parturients.[21,22,23,24,25]

Schwartz and Eisenkraft[19] described GA for cholecystectomy in a seven-year-old child with Noonan syndrome and idiopathic hypertrophic subaortic stenosis. Although the patient had a potentially difficult airway, regional anesthesia was excluded due to fears of worsening cardiovascular function from vasodilation, combativeness due to mental retardation, and potential technical problems inducing regional anesthesia. The patient therefore was anesthetized using a halothane inhalation induction and paralyzed only after the ability to manually ventilate the patient's lungs was confirmed. Intubation was achieved with the aid of an introducer and the operation proceeded uneventfully.

Campbell and Bousfield[20] reported a five-year-old patient with increasing spasticity in both legs requiring GA for computed tomography (CT) scan and myelography. One of the major anesthetic concerns was hypertrophic cardiomyopathy with dynamic left ventricular (LV) outflow obstruction (due to septal hypertrophy). As intubation was not anticipated to be problematic, anesthesia was induced with thiopental, alfentanil, and atracurium. The trachea was intubated easily and anesthesia was maintained with nitrous oxide, oxygen, and isoflurane. As the procedure was short, noninvasive monitoring was used, and hemodynamic stability was maintained. Four weeks later, the patient required a similar GA for a lumbar laminectomy and division of filum. During this procedure, invasive arterial and central venous monitoring were used and recovery was uneventful. Regional anesthesia for young children is rarely an option and "awake" airway control or establishing invasive monitoring may be difficult without sedation. Clearly, in this case, achieving hemodynamic stability was a key objective. Ketamine may not be an ideal induction agent since it can increase myocardial contractility, accentuating LV outflow obstruction, which reduces stroke volume.

Of the six parturients with Noonan syndrome, four required cesarean section (C/S). The case described by Dadabhoy and Winnie[21] was a parturient who underwent elective C/S for cephalopelvic disproportion. Although the patient had the characteristic appearance of Noonan syndrome, she did not exhibit marked respiratory dysfunction and had no evidence of cardiac abnormalities or mental retardation. The patient was thought to have a difficult airway and, therefore, regional anesthesia was chosen. As the epidural space was difficult to locate, a spinal anesthetic was performed, producing a high (T1) block with associated hypotension readily controlled with intravenous (i.v.) crystalloids and ephedrine.

Two others parturients required emergency C/S.[22,23] The first was a 25-year-old with severe residual cardiac disease despite previous corrective cardiac surgery as a child.[22] During her admission she was noted to have mitral stenosis, a hypoplastic pulmonary valve, impaired LV function, and a dilated left atrium. Pregnancy was complicated by an episode of fast atrial fibrillation, successfully treated with digoxin, beta-blockade and thromboprophylaxis. She developed pulmonary edema and antepartum hemorrhage (APH). Unfortunately, at 30 weeks' gestation, she had an intrauterine death so labor was induced to expedite delivery. As there was no evidence of coagulopathy, lumbar epidural analgesia (LEA) was administered using 0.1% bupivacaine. This enabled a reduction in any detrimental sympathetic stimulation and minimized variations in heart rate, contractility, and filling pressures. Due to failed induction of labor, she underwent a C/S under GA following an awake, oral fiberoptic intubation. Magboul[23] described a patient without cardiac disease requiring an emergency C/S under subarachnoid block (SAB). Although a reduced dose of subarachnoid lidocaine was used, a satisfactory block was obtained for the procedure. The author suggested that in these cases, the bony vertebral spinal canal may be narrowed with a normal caliber cord. This narrowing might reduce the size of the epidural and subarachnoid spaces, increasing spinal spread. In addition, the patient was short and had significant kyphoscoliosis and lumbar lordosis, which would have contributed to the unpredictable SAB. However, it may be argued that, as the patient was known to be difficult to intubate (severe fused and webbed neck, micrognathia, and Mallampati grade IV view), a reduced spinal dose of local anesthetic would have been problematic if the SAB were insufficient for C/S. A combined spinal–epidural (CSE) or carefully titrated continuous subarachnoid anesthetic would be better alternatives.

Two cases involved parturients with Noonan syndrome and associated cardiac disease.[24] Although both cases had characteristic Noonan facies, vertebral abnormalities were not reported in either case. The first case involved a 22-year-old with known pulmonary and aortic stenosis. Pregnancy was complicated by premature rupture of the membranes (PROM), preterm labor, and APH. A C/S was performed at 32 weeks' gestation due to transverse lie, prolonged ruptured membranes, and fetal heart rate (FHR) decelerations. Epidural anesthesia using 2% lidocaine and sufentanil was carefully titrated with the aid of direct arterial monitoring. Surgery was uneventful, although the neonate was discovered later to have isolated congenital cardiac disease. The second case was a patient with a known coarctation of the aorta (gradient 55 mmHg). Hypertension was controlled with atenolol and labor induced at 38 weeks' gestation. Pregnancy progressed normally and labor analgesia was provided using a CSE technique, followed by a continuous low-dose epidural infusion of bupivacaine and fentanyl. To prevent the hemodynamic stresses of prolonged pushing, a vacuum extraction was performed, and mother and baby made uneventful recoveries. Adequate prenatal assessment, a multidisciplinary approach, appropriate cardiac monitoring, and antibiotic endocarditis prophylaxis are important in these women.

Another woman with Noonan syndrome required a dilation and curettage for postpartum bleeding after a normal vaginal delivery.[25] The main anesthetic concerns were a potentially difficult intubation, pulmonary valve dysplasia, mental retardation, factor XI deficiency, and thrombocytopenia. Labor analgesia was provided by i.v. patient-controlled analgesia (PCA) (fentanyl 25 μg bolus, five-minute lockout). Although LEA is considered the analgesic method of choice, it was thought to pose too great a risk of spinal hematoma in the face of a bleeding diathesis. This risk was carefully balanced against the risk for a potentially difficult intubation, should emergency C/S have been required. Following delivery, she continued to bleed vaginally (1200 ml in four hours) despite oxytocin. In order to examine her and

determine the source of bleeding, GA was induced following awake direct laryngoscopy using cautious sedation. In addition, she was given 15 μg of 1-deamino-8-D arginine vasopressin (DDAVP), which is a nonspecific adjunct that improves coagulation by increasing von Willebrand factor and factor VIII. It also increases the adhesion and spread of platelets at the injury site. The woman made an uneventful recovery.

Neurocutaneous disorders

Neurofibromatosis

Neurofibromatosis is an inherited disorder affecting neurocutaneous tissue, (also see Chapter 11). Two distinct forms of the disease exist: neurofibromatosis type 1 (NF1 or von Recklinghausen disease) and neurofibromatosis type 2 (NF2). Although both diseases have some common characteristics, they differ genetically and clinically. Neurofibromatosis type 1 occurs more frequently, accounting for up to 85% of patients with the disease. In fact, NF1 is the commonest autosomal dominant disorder affecting approximately 1:3000 births.[26] The NF1 gene, located on chromosome 17q11.2,[27] has a high spontaneous mutation rate, with 50% of cases being sporadic.[28,29] Although penetrance is complete, the gene has a varied expression (i.e. the severity of the disorder will vary among individuals). Neurofibromatosis type 1 is a progressive disease such that excessive proliferation of neural crest elements (Schwann cells, melanocytes, and fibroblasts) occurs in virtually every organ system (see Table 8.3). In order to make a diagnosis of NF1, at least two of the following criteria must be present:[30]

- six or more café-au-lait spots exceeding 5 mm in diameter in prepubertal and 15 mm in postpubertal individuals
- two or more neurofibromas of any type or one plexiform neurofibroma
- freckling in the axillary or inguinal regions
- optic glioma
- two or more Lisch nodules (benign melanotic iris hamartomas)
- a distinctive bony lesion such as dysplasia of the sphenoid bone or thinning/dysplasia of the long bone cortex with or without pseudoarthritis
- a first degree relative with NF1 (with the above criteria).

Café-au-lait spots are flat hyperpigmented macules, which increase in number and size during childhood. Neurofibromas are benign tumors consisting of a mixture of Schwann cells, fibroblasts, and mast cells. There are four distinct types of neurofibroma: cutaneous, subcutaneous, nodular, and plexiform. Cutaneous (soft, fleshy) and subcutaneous (firm, tender) neurofibromas arise from the peripheral nerve sheath and have no malignant tendencies. Nodular lesions also arise in peripheral nerves and although they can cause compression effects due to increasing size, they do not infiltrate the surrounding tissue. In contrast, a plexiform neurofibroma usually involves multiple and longer segments of nerves, and resection is difficult due to invasion. Plexiform lesions may undergo malignant change to neurofibrosarcoma in 2–16% of NF1 patients.[31] In addition to neurofibromas, patients with NF1 are at increased risk of developing benign and malignant tumors.[32] Mutations of the

Table 8.3 Clinical features of neurofibromatosis 1

Organ	Disease process	Anesthetic implications
CNS	Neurofibromas	Intellectual impairment (5–40% usually mild)
	Meningiomas, gliomas (5–10%)	Raised ICP, hydrocephalus, seizures
	Cranial nerve fibromas	Altered gag/swallowing reflexes
	Spinal nerve fibromas	Spinal-cord compression Difficulties with regional techniques
Skin	Café-au-lait spots (99%)	
	Cutaneous neurofibromas	Depending on site:
	Subcutaneous neurofibromas	Difficult IV access
	Nodular neurofibromas	Difficult regional techniques
	Plexiform neuromas	
Lungs	Mediastinal/intercostal neurofibromas	Impaired respiratory function/SVC obstruction
	Nonspecific fibrosis	Right ventricular failure
Kidney	Renal carcinoma	Renal dysfunction
	Neurofibromas	Ureteric/urethral obstruction
CVS	Congenital heart disease (especially pulmonary stenosis)	Depends on lesion: Risk of endocarditis
	Hypertension (5%)	Consider pheochromocytoma or renal artery stenosis
Pharynx Larynx	Neurofibromas	Airway obstruction Dysphagia (increased risk of aspiration) Difficult intubation
Bone	Neurofibromas	Difficult regional technique
	Fractures	
	Kyphoscoliosis (2%, mostly cervicothoracic)	Difficult intubation
Adrenal	Pheochromocytoma (0.1–5.7%)	Hypertensive response
GIT	GIT tumors	Pain, hemorrhage, perforation
	Carcinoid tumors	Carcinoid syndrome

CNS = central nervous system; ICP = intracranial pressure; IV = intravenous; SVC = superior vena cava; CVS = cardiovascular system; GIT = gastrointestinal tract.

NF1 gene result in loss of a functional protein (neurofibromin), which normally has a tumor suppressor role. Malignancies associated with NF1 include optic glioma, astrocytoma, brainstem glioma, juvenile chronic myeloid leukemia, neurofibrosarcoma, rhabdomyosarcoma, medullary thyroid carcinoma, intestinal tumors, and pheochromocytoma.[33] Other associated conditions include short stature, kyphoscoliosis, learning disabilities, hypertension, hydrocephalus, seizures, and various congenital abnormalities (pulmonary stenosis, spina bifida, rib, and vertebral anomalies).

Neurofibromatosis type 2 is genetically and clinically distinct from NF1, with the responsible gene located on chromosome 22q12.1. It is considerably rarer than NF1 with an approximate incidence of 1:50 000 births. Manifestations include bilateral acoustic neuromas in 95% of cases, and other CNS tumors such as meningiomas and gliomas.[34] In common with NF1, it is inherited in an autosomal dominant manner, with 50% of cases resulting from spontaneous mutation.

The following criteria are required to make a diagnosis of NF2:[30]

- bilateral vestibular schwannomas (bilateral "acoustic neuromas"), or
- history of NF2 in first-degree relative plus any two of the following:
  - meningioma
  - glioma
  - schwannoma
  - juvenile posterior subcapsular lenticular opacities
  - juvenile cortical cataract.

Cutaneous lesions such as café-au-lait spots and neurofibromas are seen in up to 70% of patients with NF2, although plexiform neuromas are not seen.

Neurofibromatosis in pregnancy

Although NF has no detrimental effect on fertility in women, pregnancy itself poses an increased risk to the parturient and her fetus. Neurofibromas are known to increase in number and size during pregnancy and regress in the postpartum period. It is speculated that there may be a link between the growth of neurofibromas and levels of circulating hormones because progesterone, estrogen, and growth hormone receptors are all found in neurofibromatous tissue.

Other detrimental effects to the parturient include: presence of pelvic/abdominal neurofibromatas making C/S necessary (dystocia, obstructed labor or respiratory embarrassment),[35] predisposition to hypertension,[36] possible death from undiagnosed pheochromocytoma, renal artery stenosis and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome,[37] renal artery rupture or other vascular complications, and, rarely, malignant degeneration of neurofibromata.[38] Posma[38] described a case of a malignant mediastinal schwannoma in a parturient, who required a therapeutic abortion in order to undergo radiotherapy for the treatment of her tumor. During her second pregnancy, despite being in remission for over three years, she developed a recurrence and died shortly after giving birth. Detrimental effects to the fetus include: increased risk of spontaneous abortion, stillbirth, intrauterine growth restriction (IUGR), and preterm labor.[35,39]

Anesthetic management

Both GA and regional (spinal, epidural) anesthesia have been used successfully in patients with NF.[40,41,42] A thorough assessment of the patient is necessary to exclude the features outlined in Table 8.3. If regional anesthesia is contemplated, key areas of concern include the presence of raised intracranial pressure (ICP), spinal tumors, and kyphoscoliosis. Dural puncture, in the presence of raised ICP, or direct trauma to a spinal neurofibroma from an epidural or spinal needle may have disastrous consequences. Although lumbar neurofibromas are usually unilateral, they can be large, asymptomatic, and extend towards the midline making them vulnerable to direct needle trauma. Despite the majority of asymptomatic patients having no spinal involvement, it is prudent to avoid neuraxial anesthesia unless recent radiological scans exclude a spinal lesion. Some recommend magnetic resonance imaging (MRI) or CT of the brain and spinal cord late in pregnancy, as tumors may grow significantly during gestation.[43] One case of LEA in a parturient with NF was complicated by dural puncture and subsequent epidural hematoma. Fortunately, the patient made a full recovery with conservative treatment, but the case highlighted communication problems and the need for a thorough assessment prior to anesthetic management.[43]

As pheochromocytoma complicates 0.1–5.7% of patients with NF1,[44] it is vital to exclude this condition, particularly in those patients with sustained or paradoxical hypertension resistant to treatment. If GA is considered, the main areas of concern include the possibility of a difficult intubation and/or airway obstruction.[45] Neurofibromas may involve the tongue, larynx, or trachea and cause airway obstruction and difficult intubation. Plexiform neurofibromas occur commonly in the cervical region and may distort the airway. Symptoms of dyspnea, stridor, or change in voice should alert one to potential airway problems. Even if recognized early, elective awake fiberoptic tracheal intubation may not be successful due to the distorted anatomy. Neuromuscular blocking drugs can be used in normal doses in patients with NF.[46]

Tuberous sclerosis (Bourneville-Pringle disease)

Tuberous sclerosis (TS) has been described as a triad of seizures, mental retardation, and a central facial skin eruption (mislabeled "adenoma sebaceum"), but it is clearly a multiorgan disease.[47] Pathology consists of a hamartomatous proliferation in the brain, spinal cord, skin, kidney, eyes, heart, lungs, and bones (see Table 8.4). This slowly progressive disease is inherited in an autosomal dominant manner with variable expression. The incidence is quoted as 1 in 5000–10 000 births; however, as there is a wide expression in the severity of the disease, the true incidence and prevalence is unknown. Causative mutations in two separate genes have been found in patients with TS, one located on chromosome 9q34 and the other on 16p13.3.[48] Only one third of cases are familial. In order to make a diagnosis of TS at least two major features or one major and two minor features must be present:[47]

Major features:

- facial angiofibromas, formerly called "adenoma sebaceum"
- Shagreen patch (connective tissue nevus mostly over trunk)

Table 8.4 Clinical features of tuberous sclerosis

Organ	Disease process	Anesthetic implications
Brain	Cortical hamartomas (gyri & subependymal)	Epilepsy (80%)
	Astrocytomas (15%)	Mental retardation (mild to severe 70%)
	Calcification	Focal neurological signs
		Hydrocephalus
Skin	Hypopigmented macules (ash-leaf spots) (90%)	Nil
	Red/yellow papules (central face-"adenoma sebaceum" (90%))	
	Shagreen papules-lumbosacral (40%)	
	Café-au-lait spots (12%)	
	Periungal fibroma (40%)	
Kidney	Renal hamartoma (angiomyolipomas) (65%)	Deterioration of renal function
	Cysts	Pain/hemorrhage into cysts
Eyes	Retinal hamartomas (50%)	Nil
Heart	Rhabdomyomas (50%)	Conduction defects, dysrhythmias, congestive heart failure, risk of endocarditis
Lungs	Smooth muscle hamartomas (lymphangiomyomas) (1%)	Progressive deterioration of lung function
	Cysts	

- three or more hypomelanotic macules (ash-leaf spots – elliptical in shape)
- nontraumatic ungula or periungual fibroma
- lymphangioleiomyomatosis (also known as lymphangiomyomatosis)
- renal angiomyolipoma
- cardiac rhabdomyoma
- multiple retinal nodular hamartomas
- cortical tumor
- subependymal nodules
- subependymal giant cell astrocytoma.

Minor features:

- confetti skin lesions (multiple 1–2 mm hypomelanotic macules)
- gingival fibromas
- multiple randomly distributed pits in dental enamel
- hamartomatous rectal polyps
- multiple renal cysts
- nonrenal hamartomas
- bone cysts
- retinal achromic patch
- cerebral white matter radial migration lines.

The morbidity and mortality of cardiac rhabdomyomas is determined by flow abnormalities if they are of a sufficient size to impair cardiac outflow. Coarctation of the aorta, constriction of the major arteries (e.g. renal stenosis), and aortic aneurysm are all associated with TS. The main neurological lesions are due to hamartomas, with giant cell tumors (astrocytomas) occurring in 10–15% of patients with TS. These patients typically present with signs and symptoms of hydrocephalus or focal neurologic signs. The majority of patients with TS have neurologic abnormalities, including cognitive deficits, learning disabilities, and seizures. The extent of cerebral dysfunction is directly related to the number of cortical tubers. The pulmonary manifestations of the disease include lymphangioleiomyomatosis (LAM), which is a condition in which there is hamartomatous proliferation of the smooth muscle of the respiratory bronchioles, pulmonary arterioles, and pulmonary lymphatic vessels.[49] The onset of LAM occurs mostly between 30–40 years, coinciding with the age of parturients. Although progression of LAM is variable, it has a poor prognosis, resulting in significant limitation of lung function due to destruction of lung tissue from hamartomatous cavitation. The commonest presentations are dyspnea and pneumothorax (from rupture of peripherally located cysts into the pleural space). Tuberous sclerosis is associated with a variety of benign tumors, and an increased risk of malignancy, the commonest being cerebral tumors and rhabdomyosarcomas.

Effect of pregnancy on the disease

There are several reported cases of tuberous sclerosis in pregnancy,[50,51,52,53] and many are associated with serious maternal and fetal complications. In a study by King *et al.* 43% of women with TS had perinatal problems (see Table 8.5).[53] There was also an increased risk for fetal cardiac rhabdomyomas, which cause fetal demise if >3 cm and are associated with fetal cardiac dysrhythmias. Women with TS can also present with seizures, which could confound a diagnosis of eclampsia, since there are reports of preeclampsia in TS patients.

Despite these concerns, many women with TS have uncomplicated pregnancies.[54] However, having prior knowledge of the full extent of the disease (organ involvement) will allow one to be prepared for a potentially complicated pregnancy. Renal involvement can be associated with a poor prognosis and patients with renal angiomyolipomas are at risk of profound hemorrhage.[55]

Anesthetic management

There are a limited number of case reports concerning the management of anesthesia in adult patients with TS.[56,57,58] Although several parturients described in case reports required labor analgesia or anesthesia for instrumental delivery, the reports failed to detail specific anesthetic management. Of importance to the anesthesiologist is a history of seizures, mental retardation, focal neurological signs, hydrocephalus, renal dysfunction, ventricular dysfunction, dysrhythmias, and poor pulmonary function.

Table 8.5 Perinatal problems with tuberous sclerosis

Maternal
- Skin lesions
- Mental retardation
- Seizures
- Placental abruption
- Preeclampsia
- Operative delivery
- Renal cysts (massive hemorrhage)
- Polyhydramnios

Fetal
- Preterm delivery
- Intrauterine growth restriction
- Increased perinatal death
- Cardiac rhabdomyomas

From King & Stamilio (2005)[53]

Anesthesiologists should be aware that patients with TS and neurological disease are likely to have coexisting cardiac and renal disease. Each parturient must be assessed on an individual basis and the anesthetic tailored accordingly. Of concern is the fact that renal angiomyolipomas are present in 65% of TS patients, and spontaneous rupture has been reported during pregnancy.[55] It is prudent, therefore, to have adequate i.v. access and cross-matched blood available during labor. In patients with LAM, effective LEA in labor reduces hyperventilation and excessive changes in intrathoracic pressure during contractions. An elective instrumental delivery to avoid excessive straining during the second stage may be preferable, especially if there is a history of previous nonsurgically treated pneumothorax, as the recurrence rate is high.[56] In addition, nitrous oxide should be avoided if there is evidence of noncommunicating cystic lung disease or closed pneumothorax. The presence of brain lesions (e.g. large subependymal nodules) may cause an increase in ICP, obstruction of the ventricles and difficulty controlling seizures. It is important to continue anticonvulsant medication, prevent reductions in seizure thresholds (e.g. with adequate labor analgesia), and to avoid SAB if ICP is elevated.

Von Hippel-Lindau disease

This rare (incidence 1 in 36 000), multisystem disease is characterized by a variety of benign and malignant tumors. The commonest lesions associated with von Hippel-Lindau disease (VHL) are hemangioblastomas (benign vascular tumors) involving the retina, adrenal glands, cerebellum, brain stem, spinal cord, and kidneys (see Table 8.6). [59] Other associated features include renal cell carcinomas (clear cell), pancreatic tumors, endolymphatic sac tumors of the middle ear, papillary cystadenomas of the broad ligament, and pheochromocytomas. In VHL syndrome, pheochromocytomas tend to occur in younger patients, are often extraadrenal, and are less likely to be associated with symptoms or biochemical evidence of catecholamine production.[60] Although autosomal dominant inheritance occurs, there is variable expression. The responsible gene is located on chromosome 3p25–p26, which is a tumor suppressor gene, with a second, somatic mutation required for the development of the cancer.

Table 8.6 Clinical features of von Hippel-Lindau disease

Organ	Disease process	Anesthetic implications
CNS	Hemangioblastomas involving:	Raised ICP
	cerebrum (2%)	Risk of CNS hemorrhage
	cerebellum (38%)	Seizures
	brain stem (10%)	Risk of damage by epidural/spinal needles or catheters
	spinal cord (51%)	
Retina	Hemangioblastomas (60–70%)	Nil
Kidney	Hemangioblastomas (20%)	Kidney dysfunction
	Cysts	
	Renal carcinoma	Erythrocytosis
Adrenals	Hemangioblastomas	
	Pheochromocytoma	Severe hypertensive response
Pancreas	Hemangioblastomas (20%)	Altered glucose metabolism
	Cysts	
Face	Hemangioblastomas	Possible intubation problems
Lung	Hemangioblastomas	Pulmonary dysfunction
		Pulmonary hemorrhage
Liver	Hemangioblastomas	Liver dysfunction

ICP = intracranial pressure; CNS = central nervous system

Maternal and fetal outcome data have been described in 30 women and 56 pregnancies.[61] Most pregnancies had a favorable outcome, with a 96% fetal survival and 5% maternal morbidity. Anesthetic management has been described in parturients with VHL.[62,63,64,65] Several of these parturients received epidural anesthesia and there are no reports of neurological complications.

Based on these few reported cases it is difficult to make firm recommendations regarding anesthetic technique. Due to the frequency of CNS involvement, elective C/S is the preferred mode of delivery.[66] Cesarean section avoids the risk of CNS hemorrhage secondary to an increase in cerebral blood pressure associated with the expulsive efforts of labor. Although no anesthetic method is absolutely contraindicated, management should be tailored according to associated findings (e.g. pheochromocytoma, raised ICP). It can be argued that neuraxial anesthesia should be avoided on the grounds of asymptomatic spinal cord involvement with the possibility of direct injury to a hemangioblastoma by needle or catheter. Although the spinal cord lesions are usually cervicothoracic, they may involve the lumbosacral

region or even the cauda equina. As most are located in the pia mater or posterior intramedullary cord, it is prudent to scan for such lesions prenatally. If GA is used, it is important to blunt the pressor response due to tracheal intubation, as hypertensive surges could cause CNS hemorrhage.

Myasthenia gravis

Myasthenia gravis (MG) is a chronic autoimmune disease involving the postsynaptic neuromuscular junction. The hallmarks of the disease are weakness and rapid fatigability of striated muscle with repetitive use, followed by partial recovery with rest.[67] The underlying defect is a reduction in the number of available acetylcholine receptors (AchR) at the postsynaptic neuromuscular junction, thereby producing a compromise in the end plate potential and a reduction in the safety factor for effective synaptic transmission. This defect is mediated by autoantibodies against the AchR, although the factors that initiate and maintain the autoimmune response are not fully understood. The absolute level of antiAchR antibodies correlates poorly with the disease severity, although changes in antibody levels may correlate with disease progression.

Myasthenia gravis is the commonest disorder affecting the neuromuscular junction. Prevalence of the disease appears to be increasing, probably due to an aging population and ranges from 12–64 cases per million (average 0.004%).[68] Overall, women are affected twice as often as men, and although MG can occur at any age, there is a bimodal peak of incidence. The first peak, in the third decade, affects mostly women, whereas the second peak is in the sixth and seventh decades, and affects mostly men. Familial cases are uncommon and no consistent HLA type or genetic inheritance pattern has been identified.[69] However, ethnic differences do occur, with Asians more likely than Caucasians to have type 1 MG presenting in childhood. There are some HLA associations between different ethnic groups.[70]

The Osserman classification system is the most commonly used clinical classification for MG (see Table 8.7). Diagnosis is made on clinical grounds (i.e. fatigable muscle weakness without loss of deep tendon reflexes or other neurological symptoms), coupled with pharmacologic and electrophysiologic tests. Muscle weakness varies in distribution and on the time of day, with more profound weakness occurring at the end of the day.

There is no single test adequate for diagnosis and therefore clinical history and a combination of tests are used: acetylcholine antibody assay, edrophonium test, and electromyography (EMG).[71] Serum AchR binding antibodies are present in 85% of all MG patients, with negative results more likely in those patients with mild or only ocular disease. However, the use of multiple AchR tests (e.g. binding, blocking, modulating antibodies) may decrease the number of seronegative MG patients. Once a muscle group has been shown to weaken with exercise and improve with rest, the use of the cholinesterase inhibitor edrophonium test can contribute to the diagnosis of MG. Improvement in muscle strength after administration of the drug supports the diagnosis; however, due to increased muscarinic effects of acetylcholine (Ach), side effects may include bradycardia, asystole, and bronchoconstriction. All patients undergoing the test should be monitored with an ECG with full resuscitation equipment available in case a severe cholinergic reaction occurs (e.g. sweating, bradycardia, hypotension, increased weakness, increased respiratory secretions, and laryngospasm). The edrophonium test is not specific for MG and false positives occur with other disease entities such as amyotrophic lateral sclerosis, botulism, Guillain-Barré syndrome, and end-stage renal failure. In addition, false negatives occur with 40% of patients presenting with eye signs alone.[72] The edrophonium test can distinguish between a "myasthenic" and a "cholinergic" crisis in a patient on high doses of anticholinesterase medication and increasing muscle weakness.

Table 8.7 Clinical classification of myasthenia gravis

Type 1	Extraocular muscles involved only (10% of patients with MG)
Type 2a	Mild, generalized myasthenia No respiratory crises
Type 2b	Moderate, generalized myasthenia No respiratory crises
Type 3	Severe Acute onset, rapid deterioration (<6 months) Respiratory crises
Type 4	Severe Slower onset (>2 years) Respiratory crises

MG = myasthenia gravis

Repetitive supramaximal motor nerve stimulation by EMG shows a characteristic fade in amplitude of the evoked action potential in patients with MG. In order to increase the sensitivity of the test, several muscle groups should be investigated and anticholinesterases should be stopped before testing. This test is sensitive to muscle temperature, movement artifact and is less likely to be positive in patients with type 1 MG.

The course of the disease is highly variable but usually progressive, although exacerbations and remissions do occur. The progression of weakness in MG usually occurs in the cranial-to-caudal direction: ocular-to-facial-to-lower bulbar-to-truncal-to-limb muscle. Exacerbations may occur spontaneously or be associated with predisposing factors (see Table 8.8). Good prognostic indicators include female, white race, early age of onset, long duration of purely ocular symptoms, and spontaneous remissions lasting longer than one year.[70] Some reports suggest that 40–50% of patients with type 1 (purely ocular) disease will develop the generalized condition within two years.

Current treatment of MG includes enhancing neuromuscular transmission by anticholinesterase medication; suppressing the immune system with corticosteroids and azathioprine; decreasing circulating antibody level by plasmapheresis; or thymectomy.[73,74]

Anticholinesterases increase the amount of Ach available at the neuromuscular junction and are the first line of treatment for most patients with MG. The most commonly used anticholinesterase is pyridostigmine due to its pharmacological profile (onset

Table 8.8 Predisposing factors that exacerbate myasthenia gravis

Infection
Exertion
Menstruation
Emotional stress
Acute illness
Pain
Excessive heat or cold
Surgery/trauma
Underdosing of anticholinesterase medication
Malnutrition
Hyper-/hypothermia
Drugs
Antibiotics (presynaptic block) – aminoglycosides, tetracycline, erythromycin
Antidysrhythmics – beta-blockers, calcium channel blockers
Magnesium (pre- and postsynaptic block)
Beta-agonists (hypokalemia)
Thyroxine
Penicillamine (immune mechanism)
Lithium
Phenytoin
Diuretics (e.g. furosemide [hypokalemia])
Corticosteroids (steroid-induced myopathy)
Chloroquine

Clearly the need to take one of the above drugs may take precedence over the risk of worsening of myasthenia gravis symptoms.

10–15 minutes, offset four hours). A slow-release preparation is available for the few patients who experience severe morning weakness. At high doses, pyridostigmine can cause muscle weakness through its effects on nicotinic receptors. However, due to the use of current combined treatment therapies, high doses of pyridostigmine are rarely required.

Immunosuppressive therapy is directed at reducing the production of antibodies. Corticosteroids produce remission in 30% of MG patients, with significant improvement in symptoms in up to 45% of the rest. In some patients symptoms get worse, transiently, for the first three weeks of corticosteroid therapy. Azathioprine blocks cell proliferation and is thought to work by inhibition of T lymphocytes. The major disadvantage of azathioprine is the prolonged time to clinical effect, and so it is used in combination with corticosteroids to improve efficacy. Cyclosporine offers little advantage over azathioprine, although it lowers AchR antibodies more rapidly. In one study, the use of the immunosuppressant mycophenolate resulted in a 73% symptom improvement in patients refractory to other treatments, and with fewer side effects.[75]

Plasmapheresis and i.v. immunoglobulin (IVIg) are equally effective for treatment of MG exacerbations.[76] Plasmapheresis is thought to remove the circulating AchR antibodies, although improvement also has been reported in seronegative patients. Adverse effects include complications of central venous catheters and hypotension.

Intravenous immunoglobin consists of pooled immunoglobulins (specific, monoclonal antibody to B cell antigen CD 20), and is thought to work by down-regulating the immune system. Improvement has been reported to occur in 75% of patients, beginning within days and lasting up to eight weeks.[77]

Thymectomy is recommended for all patients with MG that is secondary to thymoma irrespective of the severity of the disease. It is also recommended in nonthymomatous autoimmune MG, as an option to increase the chance of remission or to improve symptoms.[76] Up to 75% of MG patients have pathological abnormalities in the thymus (85% thymic hyperplasia, 15% thymoma). The reason for improvement in MG following thymectomy is not fully understood. However, it is known that cell-mediated immunity, which is expressed through the T lymphocyte system and dependent on the thymus, plays a role in the pathogenesis of MG.

Effect of pregnancy on myasthenia

The course of MG is unpredictable during pregnancy; however, worsening of symptoms tends to occur more frequently in the first trimester and postpartum period.[78] The effect of pregnancy on MG cannot be predicted from its course during previous pregnancies or from any feature of the maternal disease.[79] Complete remission has been described in some patients during late pregnancy.

Puerperal infections increase exacerbations of MG and therefore should be diagnosed and treated promptly. The incidence of clinical exacerbations appears lower in those women who had thymectomy before pregnancy.[80] Maternal mortality is more likely in the first year of disease, and least likely after seven years from the onset of MG. The long-term outcome of the disease is not altered by pregnancy.

Effect of myasthenia on pregnancy

Myasthenia does not affect fertility and its reported incidence in pregnancy ranges from 1:10 000 to 1:50 000.[78] Women with MG have an increased risk for pregnancy complications and adverse pregnancy outcomes.[81] Maternal risks include respiratory failure, adverse drug response, myasthenic exacerbations and crisis (an exacerbation requiring mechanical ventilation).

Perinatal mortality has been reported to be as high as 68/1000 live births, secondary to neonatal MG and fetal anomalies. The transplacental transfer of antiAchR antibodies to the fetus may be responsible for transient neonatal MG found in 10–20% of newborns. The occurrence of neonatal MG is halved if the mother has had a thymectomy.[81] Although there is some correlation between the occurrence and severity of neonatal MG and high AchR antibody titers, some women without elevated AchR antibodies have had babies with neonatal MG.[82] All babies born to myasthenic mothers should be carefully monitored for signs of muscle weakness. Symptoms commonly occur in the first 12–24 hours after delivery and include poor sucking, difficulty in feeding, generalized hypotonia, floppiness, weak Moro reflex, feeble cry, ptosis, and respiratory distress. Complete recovery is

Table 8.9 Equivalent dosages of anticholinesterase medication

Drug	Duration of action	Intravenous dose	Intramuscular dose	Oral dose
Pyridostigmine	4–6 hours	1–2 mg	1–2 mg	30–60 mg
Neostigmine	2–3 hours	0.5 mg	1.5 mg	15 mg

Physostigmine is not used as it crosses the blood–brain barrier and causes central stimulation.
Pyridostigmine is preferred anticholinesterase as it has less muscarinic side effects than neostigmine.

expected in less than eight weeks in 90% and by 16 weeks in the other 10% of babies.[83] Anticholinesterase drugs and ventilatory support may be necessary in some cases. The perinatal death rate due to fetal anomalies is significantly higher than in the normal population. Severe birth defects were observed in 3.9% of the 127 newborns of MG mothers compared with 1.9% in a control group.[84]

Obstetric management

This high-risk pregnancy should encompass a multidisciplinary approach involving obstetrician, anesthesiologist, pediatrician, and neurologist. The key to prenatal management includes increased rest, prompt treatment of infection, proper titration of medication, alertness for exacerbations, and avoidance of predisposing factors (see Table 8.8).[78] Myasthenia gravis therapy for parturients should be chosen after evaluating the severity of the disease against possible fetal side effects. No fetal problems have been attributed to anticholinesterase medications, since they do not cross the placenta readily. The fetal risks of immunosuppressant drugs are listed in Chapter 22. Plasmapheresis and IVIg have been used safely in pregnancy, mainly for short-term management of exacerbations.[76]

During pregnancy, dosage adjustments of medications are frequently necessary due to the physiological changes of expanded plasma volume, increased renal excretion, and hepatic stasis. This may be compounded by erratic gastrointestinal absorption, especially when nausea, vomiting, or increased bulbar involvement are present. Anticholinesterases may have to be administered parenterally during the first trimester if emesis is an issue. Parenteral administration avoids the problem of variable gastric absorption and should minimize breakthrough symptoms caused by subtherapeutic levels (see Table 8.9).

If thymectomy is deemed necessary, it should be planned prior to conception, as there is no advantage in incurring the added operative risk during pregnancy even though thymectomy has been performed successfully during the first trimester.

Most parturients can deliver vaginally although one study reported a higher number of C/S in women with MG.[81] Myasthenia does not affect the first stage of labor because the uterus consists of nonstriated muscle. However, during the second stage, striated muscles are required and instrumental delivery may be required due to fatigue.[79] Neostigmine, given intramuscularly or i.v., is preferred despite its shorter half-life, as pyridostigmine may cause a sterile abscess at the injection site. Corticosteroids should be continued and supplemental doses may be required during labor or instrumental delivery.

Table 8.10 Associated problems in patients with myasthenia gravis

Muscle weakness	Bulbar/oropharyngeal → pooling of secretions and saliva → respiratory obstruction and aspiration
	Respiratory → difficulty in clearing secretions → respiratory failure
Associated conditions	Thymus hyperplasia (75%), thymoma (10–25%) and other malignancies
	Thyroid disease (3–15%)
	Systemic lupus erythematosus (2%)
	Rheumatoid arthritis (4%)
	Ankylosing spondylitis
	Crohn disease
	Hypertension
	Diabetes mellitus
	Myocarditis → cardiomyopathy, dysrhythmias
	Seizures

Hypermagnesemia causes neuromuscular blockade by inhibiting the release of Ach, reducing the depolarizing action of Ach at the end plate and depressing muscle fiber membrane excitability. Therefore, magnesium sulfate ($MgSO_4$) should not be used in patients with severe MG (for tocolysis or preeclampsia), and if considered in mild MG should be used with great caution. Maternal deaths in MG parturients have occurred from the use of $MgSO_4$ for preeclampsia.

Most myasthenic mothers can safely breast feed. However, it may be prudent to avoid breast feeding in symptomatic neonates, as AchR antibodies can potentially pass into the breast milk and enhance neonatal MG. Breast-feeding should also be avoided in those mothers taking azathioprine and mycophenolate mofetil.

Anesthetic management

Some of the problems facing the anesthesiologist are listed in Table 8.10. It is important to perform an extensive, *early* evaluation of the patient. Particular importance should be paid to onset, duration, severity (especially bulbar and respiratory muscle involvement), disease treatment, and associated diseases (see Table 8.11). An EKG should be obtained because there are reports of focal myocardial necrosis in some MG patients. Preoperative lung function testing may identify patients at particular postoperative risk. Women with a forced vital capacity < 40 ml/kg or 2.9 L are more likely to require prolonged respiratory support. Optimizing their condition will decrease the risk of surgery and improve outcome.[85]

Table 8.11 Relevant assessment of the patient with myasthenia gravis

History	Tests
Difficulties: chewing, swallowing	Hemoglobin Urea and electrolytes May have decreased nutritional intake
Difficulties: coughing, clearing secretions	Chest radiograph (? chronic aspiration)
Difficulties: clear/loud speech	Bulbar problems
Dyspnea: rest/exercise	Arterial blood gases Pulmonary function tests (e.g. vital capacity)
Cardiac symptoms	Electrocardiogram
Thyroid dysfunction symptoms	Thyroid function tests
Neurologic symptoms	Full neurologic examination
Medication side effects	

Regional anesthesia is the preferred method of analgesia for labor and delivery[86,87,88,89] since it avoids opioid-induced respiratory depression and allows flexibility should operative delivery be necessary. Regional anesthesia is favored for C/S unless the patient has significant respiratory compromise or bulbar involvement that dictates securing the airway prior to surgery. Combined spinal–epidural analgesia has been used successfully for labor and delivery in a woman with severe MG.[87] Ester local anesthetics may have a prolonged half-life due to the decreased cholinesterase activity in patients on anticholinesterase medication. This may lead to problems with local anesthetic toxicity or extensive epidural block. Therefore, amide local anesthetics are recommended for epidurals and spinals. Intrathecal and epidural opioids can be used with appropriate postoperative monitoring for respiratory depression. Should GA be necessary, it can be performed safely provided the patient is optimally prepared and neuromuscular function is adequately monitored during and after surgery.

It is controversial whether anticholinesterase medication should be maintained or discontinued preoperatively. Problems of continuing therapy include potentiation of vagal responses, inhibition of plasma cholinesterase (hence prolongation of ester local anesthetics and succinylcholine), and possible cholinergic crisis. However, in a patient who is physically or psychologically dependent or who has more than ocular symptoms, it is better to continue medication.

Another important issue is preoperative measurement of muscle strength for postoperative comparison. The disease, rather than the neuromuscular block, may prevent patients with myasthenia from reaching full strength, despite treatment. Therefore, before the administration of anesthetic drugs that may interfere with neuromuscular transmission, a control EMG or train-of-four should be recorded.

Ketamine, thiopental, and propofol have been used successfully for induction of GA in these patients.[90,91] Cardiac and vascular tone is unaffected in MG and increased cardiovascular depression has not been reported at induction.

Depolarizing and nondepolarizing muscle relaxants (NDMR) have been safely administered, although in altered doses. Because there are fewer Ach receptors in MG patients, succinylcholine, which acts by depolarizing the neuromuscular junction, may not effectively depolarize the end plate. This may result in "resistance" to the effective dose (ED95 = 2.6 × normal)[91] and an increased incidence of phase II block. Because the dose of succinylcholine commonly administered to normal patients (1–1.5 mg/kg) represents three to five times the ED95, it is likely this "resistance" is not clinically significant.[92] Anticholinesterases decrease plasma cholinesterase activity and may cause a delay in hydrolysis of succinylcholine and potentiation of neuromuscular block. Plasmapheresis may decrease the amount of circulating plasma cholinesterase producing a similar effect. Myasthenic patients are more sensitive to NDMR. Dosing should start at about one-tenth of the usual recommended doses and agents with short or intermediate half-life should be used (e.g. atracurium, vecuronium). Because mivacurium is metabolized by pseudocholinesterase its use is relatively contraindicated. The abnormal response to muscle relaxants also is seen in patients with localized ocular disease or in patients during remission.[93] Reversal of neuromuscular block may be spontaneous to avoid drug reactions or small doses of neostigmine (0.5 mg) may be given. Patients undergoing GA should be informed of the possible need for prolonged postoperative mechanical ventilation.[94]

Worsening of symptoms during the postpartum period can occur, so the patient should remain in a high-dependency unit.

Friedreich ataxia

Friedreich ataxia (FA) is a progressive, cardio- and neurodegenerative disorder that affects both the central and peripheral nervous systems. Prevalence of FA is estimated to be 1: 29 000–50 000, making it the commonest inherited ataxia.[95] The incidence is higher in Caucasians, with males and females affected equally. It is transmitted by autosomal recessive inheritance and is caused by GAA trinucleotide repeat expansion, or point mutations, in the frataxin gene on chromosome 9q13. This mutation causes a reduction in frataxin, a highly conserved protein, found in prokaryotes and eukaryotes, which is required for efficient regulation of cellular iron homeostasis.[96] In health, frataxin is found in high quantities in the brain, spinal cord, heart, and pancreas, the organs most affected by FA. Deficiencies in this protein lead to mitochrondrial accumulation of iron, which may promote injury due to oxidative stress.[97]

The diagnostic criteria[98] and clinical problems of the disease are described in Tables 8.12 and 8.13, although molecular testing has shown that the phenotypic spectrum of FA is wider than once thought. The manifestations vary in part with the number of GAA expansions. Longer GAA repeats cause a more profound frataxin deficiency and are associated with earlier onset, shorter time to loss of ambulation, a greater frequency of cardiomyopathy, and increased severity of the disease. The major clinical manifestations of FA are neurological dysfunction, cardiomyopathy, and diabetes mellitus.

Table 8.12 Diagnostic criteria for Friedreich ataxia

Autosomal recessive inheritance
Age of onset < 25 years
Progressive gait and limb ataxia
Absent tendon reflexes in lower limbs
Electrophysiological evidence of axonal sensory neuropathy (with normal/slightly raised motor nerve conduction velocity)
Dysarthria[a]
Areflexia[a] in all four limbs
Pyramidal leg weakness[a]
Distal loss of joint position and vibration sense[a]

Criteria, except as marked, within five years of symptom onset.
[a] Eventually universal *but generally not* found in patients within five years of onset of symptoms.

The most frequent presenting symptom is an ataxic gait, although it is occasionally preceded by scoliosis or cardiac symptoms. The average age of onset of symptoms is 15 years (range 2–51 years) and time from onset to being confined to a wheelchair is 11 years (range 1–25 years). Death occurs mainly due to cardiorespiratory problems related to scoliosis and cardiac abnormalities. Histological changes in the heart consist of diffuse myocardial fibrosis and degeneration of the cardiac muscle fibers.[99] Electrocardiogram abnormalities are found in up to 95% of patients with FA, the commonest being ST or T wave abnormalities. Abnormal echocardiographic findings are detectable in many FA patients, the most frequent finding being concentric LV wall thickening and asymmetric septal hypertrophy.[99] Overt diabetes mellitus or impaired glucose tolerance was found in approximately one third of FA patients, the majority requiring insulin.[98] In addition, more than 50% of patients have progressive kyphoscoliosis.

Treatment of FA involves symptomatic support and antioxidants to reduce the free radicals. In one study, treatment with idebenone (a free-radical scavenger) appears to significantly reduce the LV mass in FA patients with hypertrophic cardiomyopathy.[100]

Effect of pregnancy on Friedreich ataxia

Advances in medical management have resulted in more women with FA attaining reproductive age. In a series of 24 pregnancies in 17 women with FA, all women delivered live babies at term.[101] Ninety-six percent delivered vaginally and only two pregnancies were complicated by preeclampsia. There was no increased risk of obstetric complications. However, although few problems with pregnancy have been reported, the superimposed physiologic changes of pregnancy have the potential to aggravate cardiorespiratory problems in FA patients. One report described a pregnancy in a woman with FA that was complicated by dyspnea and palpitations, and increasing dysarthria and arm weakness in the third trimester. No explanations for this deterioration were offered but her symptoms resolved six weeks' postpartum.[102] Another woman with FA received $MgSO_4$ as a tocolytic agent and developed severe weakness and respiratory distress. Hence, magnesium is not recommended for the management of preterm labor or preeclampsia in women with FA.[103] Indomethacin may be a suitable treatment for preterm labor but coexisting diabetes or cardiac disease may deter the use of beta-mimetic agents or calcium channel blockers.

Table 8.13 Clinical features of Friedreich ataxia

Organ	Disease process	Anesthetic implications
CNS	Ataxia	Altered response to muscle relaxants
	Dysarthria	Hyperkalemic response to succinylcholine
	Loss of deep tendon reflexes	? Unpredictable response to nondepolarizing muscle relaxants
	Posterior column signs	Muscle weakness
	Weakness/decreased muscle tone, bulbar dysfunction	Increased risk of aspiration/chest infection
	Distal muscle wasting (50%)	
	Extensor plantar response (90%)	
CVS	Cardiac muscle disease	Dysrhythmias (atrial fibrillation)
	EKG abnormalities	Cardiac compromise
	Hypertrophic cardiomyopathy	
Spine	Kyphoscoliosis (mostly thoracic)	Decreased cardiopulmonary reserve
	Possible corrective surgery (e.g. Harrington rods)	Technical problems with spinal/epidural block
Eyes	Optic atrophy (25%)	
	Nystagmus (20%)	
	Abnormal extra-ocular movements	
Ears	Sensorineural deafness (10%)	
Feet	Pes cavus ± equinovarus deformity (75%)	

Associated diseases include diabetes mellitus (10%), impaired glucose tolerance (20–30%) and increased incidence of seizures.
CNS = central nervous system; CVS = cardiovascular system; EKG = electrocardiogram

Anesthetic management

The main perioperative risk in women with FA is cardiopulmonary compromise. Heart disease at the time of presentation of FA occurs in 86–95% of patients while long-term follow-up shows cardiac involvement in 100% of patients.[99] The severity of the cardiomyopathy may not correlate with that of the neurological condition. Progressive kyphoscoliosis may produce ongoing restriction of

Table 8.14 Advantages and disadvantages of different anesthetic techniques in patients with Friedreich ataxia

	Epidural	Spinal	General
Advantages	↓ perioperative respiratory problems unless high block	Rapid onset	Good airway control in patients with gross muscle weakness
	Cardiovascular stability with slow administration	Easier technique than epidural	
	Provides excellent postoperative analgesia preventing ↓SVR and ↑HR (especially with cardiac patients)	Provides good postoperative analgesia	
Disadvantages	Technical difficulties in patients with kyphoscoliosis	Technical difficulties in patients with kyphoscoliosis	Possible succinylcholine-induced hyperkalemia
	↑ incidence of patchy block in patients with kyphoscoliosis	Sudden sympathetic block may compromise patients with hypertrophic cardiomyopathy	? ↑sensitivity to NDMR

SVR = systemic vascular resistance; HR = heart rate; NDMR = nondepolarizing muscle relaxants

pulmonary function with a decrease in vital capacity and total lung capacity. In addition, corrective surgery for scoliosis may make regional anesthesia difficult. Preoperative evaluation of the patient should concentrate on cardiac and pulmonary function with an EKG and echocardiogram in all patients and pulmonary functions tests where appropriate. Baseline neurologic deficits should be documented, especially if regional techniques are contemplated. General anesthesia[104,105,106,107] and all forms of neuraxial anesthetics (LEA, SAB, and CSE)[108,109,110,111] have been used with success in pregnant and nonpregnant patients with FA (see Table 8.14). Reports about patient responses to NDMR in FA are conflicting, although most studies indicate normal responses.[104,105,106] However, it seems prudent to use small, incremental doses of NDMR and to monitor neuromuscular block intraoperatively. Although succinylcholine has been used in patients with FA, it has the potential to produce severe hyperkalemia. Where there is severe muscle wasting or rapid progression of weakness, succinylcholine is contraindicated.

In order to avoid muscle relaxants, SAB was successfully administered for elective C/S in a parturient without cardiomyopathy.[110] Many of these patients have hypertrophic cardiomyopathy, which may be asymptomatic until sudden death. As SAB may cause precipitous hypotension, it should only be used in those patients with FA who have had an extensive cardiac assessment. Epidural anesthesia provides a good alternative with a slow incremental onset and greater hemodynamic stability.[108] Other safe alternatives for maintaining hemodynamic stability include incremental intrathecal anesthesia using a spinal catheter or low-dose administration of the intrathecal component of a CSE.[111]

Arthrogryposis multiplex congenita

Arthrogryposis multiplex congenita (AMC) refers to a heterogeneous group of disorders characterized by multiple joint contractures (distal joints more affected than proximal) with associated hypotonia and muscle-mass wasting. The deformities are present at birth and are often progressive. Frequently, there are accompanying developmental defects in both the neurological system as well as various viscera (see Table 8.15).[112] It has an incidence of 1 in 3000–10 000 live births.[113] The origin of the joint deformities are primarily neurogenic in >90% AMC (resulting from peripheral and/or central nerve dysfunction) and the rest are myogenic (resulting from primary muscular degeneration).[112] Conditions that interfere with fetal movement, such as maternal MG, may also produce neonatal AMC.[114] Although the etiology remains unknown, in the majority of cases, there is a significant reduction in the number of anterior horn cells throughout the spinal cord, particularly in the cervical and lumbar regions. Damage to the anterior horn cells typically produces weakness, atrophy of muscles, and hyporeflexia without sensory loss. In addition, demyelinization of pyramidal tracts, motor roots, and peripheral nerves has been reported. Pathological changes occurring in the myogenic type of AMC include a progressive muscular dystrophy with a reduction in both number and size of muscle fibers in addition to fibrous and fatty degeneration.[112]

The exact etiology, inheritance, and pathogenesis of AMC is unknown in most cases and there is a considerable disease spectrum and varied associated organ disorders. Most cases are sporadic and the natural history and prognosis are difficult to predict. No matter the etiology, all causes of AMC are associated with decreased fetal movements (fetal akinesia). In general, the earlier in gestation the reduction in the movements begins, the more severe the contractures become. Arthrogryposis multiplex congenita is seen primarily in the pediatric population, and pregnant patients are unusual due to the rarity of the disease, the chronic disability, and the incidence of other associated abnormalities. As a result, it is impossible to determine the effect of pregnancy on the disease and vice versa. However, the risk of thromboembolism is likely to be greater in this population in view of reduced mobility. Prophylaxis against thromboembolism should be considered in all pregnant women with AMC. Decreased respiratory reserve and skeletal abnormalities may increase the likelihood of operative and premature delivery.[115]

Table 8.15 Associated abnormalities in arthrogryposis multiplex congenita

Organ	Abnormality
Joints/extremities	Contracture-limited or fixed flexion
	Absence of patellas
	Syndactylism
	Bilateral club foot
Head/neck	Micrognathia
	High-arched palate
	Mandibulofacial dysostosis
	Craniosynostosis
	Facial abnormalities
	Tracheal stenosis
CVS	Congenital heart disease (10%) e.g. PDA, AS, coarctation of aorta, cyanotic heart disease
Spine	Vertebral abnormalities
	Kyphoscoliosis
	Spina bifida
	Sacral agenesis
Respiratory system	Restrictive lung disease
	Hypoplastic lungs
	Tracheoesophageal fistula
Genitourinary system	Renal abnormalities
	Absence of vagina/uterus
CNS	CNS abnormalities
	Increased incidence of seizures

CVS = cardiovascular system; PDA = patent ductus arteriosus; AS = aortic stenosis; CNS = central nervous system

Table 8.16 Anesthetic concerns in patients with arthrogryposis multiplex congenita

Concern	Abnormality
Airway	Difficulty due to micrognathia, high-arched palate, cervical spine deformities, facial abnormalities, muscle contractures
Associated conditions	Congenital heart disease – reduced cardiovascular reserve
	Pulmonary disease due to myopathy and scoliosis
	Renal abnormalities – altered drug handling, renal function
	Seizures
Intravenous access	Joint contractures and scarring from surgery can make intravenous access difficult
General anesthesia	*Induction agents*
	↑ sensitivity due to ↓ muscle mass
	Muscle relaxants
	Nondepolarizing
	↑ sensitivity due to ↓ muscle mass
	Succinylcholine
	Possible hyperkalemic response
	Inhalation agents
	↑ sensitivity due to ↓ muscle mass
	Increased incidence of hypermetabolism on exposure to anesthetic agents rather than actual link with malignant hyperpyrexia
Regional anesthesia	Difficulty due to skeletal abnormalities – kyphoscoliosis
	Abnormalities in spinal cord
	Altered spread of local anesthetics
	Abnormalities in cerebrospinal fluid production and reabsorption
	Medicolegal consequences of neuronal damage
	Decreased accessibility to nerves due to contractures

Anesthetic management

There are several reports in the literature on the anesthetic management of AMC patients[116,117,118,119,120] and parturients with AMC.[121,122,123] Table 8.16 outlines the major anesthetic concerns. Full assessment of the patient is necessary with particular consideration to the airway and cardiorespiratory status. Respiratory problems may arise from the myopathy and skeletal deformities. These include alveolar hypoventilation, atelectasis, restrictive respiratory pattern, decreased ability to cough, and an increased incidence of aspiration. The presence of significant scoliosis may lead to reduced lung volumes, increased work of breathing, abnormal ventilation/perfusion ratios, and hypoxemia, which may proceed to carbon dioxide retention, pulmonary hypertension, and cor pulmonale. As a result AMC patients may be sensitive to opioids and more prone to respiratory depression.

Most cases of anesthetic management of AMC patients have described the difficult airway scenario in pediatric patients. Patients with AMC may react abnormally to induction agents, inhalational agents, and muscle relaxants.[122] There have been several reports of hyperthermia in some AMC children, but it is not proven that these were malignant hyperthermia (MH). Indeed, one case series of 398 anesthetics in patients with AMC reported no cases of MH.[116] It is thought that the increase in temperature seen in some patients with AMC is due to hypermetabolism unrelated to MH.[123]

Advantages of LEA for labor include excellent analgesia, maintenance of cardiovascular and respiratory function with slow incremental doses of local anesthetic, and flexibility to provide anesthesia without resorting to GA and airway manipulation. However, identifying the epidural space may be technically difficult because of scoliosis or corrective surgery. In addition, skeletal contractures may make positioning difficult. Intravenous PCA may provide a reasonable alternative for labor analgesia, using small incremental doses of opioids.

Three cases of C/S in AMC women have been reported in the literature.[121,122,123] Quance described a 21-year-old (45 kg) wheelchair-bound patient with marked kyphoscoliosis and pelvic and lower-limb deformities, without any associated primary

Table 8.17 Classification of Ehlers-Danlos syndrome

Subgroup	Inheritance	Skin hyperextensibility	Skin fragility	Bruising/ bleeding	Joint hypermobility	Other
Classical (formerly EDS I and II)	AD	Mild–severe	Mild–severe	Mild–severe	Mild–severe	60% of all EDS
Benign Hypermobility (formerly EDS III)	AD	Mild	Mild	Mild	Severe	30% of all EDS
Vascular (formerly EDS IV)	AD	Mild	Severe	Severe	Limited to digits	Blood vessel/visceral rupture
Kyphoscoliosis (formerly EDS VI)	AR	Moderate–severe	Moderate–severe	Moderate–severe	Moderate–severe	Congenital scoliosis Eye involvement (microcornea, scleral perforation, retinal detachment), Hypotonia
Arthrochalasia (formerly EDSVII A and B)	AD	Moderate	Moderate	Mild–moderate	Severe	CHD Scoliosis Hypotonia
Dermatosparaxis (formerly EDS VII C)	AR	Moderate	Moderate	Severe	Moderate	

AD = autosomal dominant; AR = autosomal recessive; EDS = Ehlers-Danlos syndrome; CHD = congenital hip dislocation

respiratory or cardiac problems.[121] Elective C/S was planned at term due to severe pelvic deformities. The preferred epidural technique failed due to unilateral block. Spinal anesthesia was not considered because of the possibility of abnormal spinal-cord CSF dynamics and the risk of a high block. Therefore, GA was induced using thiopental, succinylcholine, and fentanyl and maintenance with oxygen, nitrous oxide, and isoflurane. The procedure was uneventful except for minimal difficulty with an unexpected grade III laryngoscopy. A possible reason for the epidural-block failure is that patients with AMC have an increased incidence of spina bifida occulta and sacral agenesis, which may affect the spread of the local anesthetic.

Rozkowski and coworkers reported successful anesthesia for a C/S using a spinal catheter to administer incremental doses of local anesthetic.[122] This particular technique was used because it was considered a safer and more predictable method of obtaining an adequate block. The only side effect was mild shortness of breath due to a high block. Spooner described a 26-year-old parturient with lumbosacral scoliosis requiring a C/S.[123] Despite difficulties in locating the epidural space, a CSE was performed successfully without perioperative complications.

Ehlers Danlos syndrome

The Ehlers Danlos syndrome (EDS) is a group of inherited connective tissue disorders, which differ clinically, genetically, and biochemically. The original classification of over ten different subgroups of EDS using Roman numerals has now been revised. An updated classification system differentiates EDS into six primary subgroups, in addition to some more rare forms of the disease.[124] Unfortunately, confusion arises as both classifications now occur in the literature.

The main features of EDS comprise skin hyperextensibility (increased elasticity and extension), joint hypermobility (increased laxity and extension of joints) and connective tissue fragility.[125] Although sharing the cardinal features of the syndrome, the severity of each varies widely among the subgroups (see Table 8.17). In addition, each subgroup of EDS represents a clinical spectrum of abnormalities. The vascular subgroup of EDS is at particular risk of premature death from arterial rupture either arising spontaneously or with trauma.[126]

The exact prevalence of EDS is unknown due to undiagnosed milder forms of this condition, although an estimate of 1:5000 has been given.[125] Ehlers Danlos syndrome is most prevalent among Caucasians, with men and women being equally affected. The commonest types of EDS are the classical (approximately 60%), hypermobility (approximately 30%), and vascular (approximately 6%) subgroups. The other types of EDS are extremely rare.

The basic defect results in deficient or defective collagen, and is caused by mutations in structural collagen genes or in genes coding for enzymes involved in their posttranslational modification. Many types of collagen occur and these proteins are essential for development and organogenesis, cell attachment, and platelet aggregation, in addition to providing tensile strength to

Table 8.18 Disease manifestastions of Ehlers-Danlos syndrome

Organ	Dysfunction	Anesthetic/surgical implication
Skin	Hyperextensibility	Scarring – difficult IV access
	Fragility	Poor wound healing – sutures hold poorly
		Fragility – careful taping/padding perioperatively
		Careful patient positioning/padding
Musculoskeletal	Hypermobility of joints, effusions, hemarthrosis, dislocations, premature degenerative joint disease	
	Spinal malalignment/ spondylolisthesis (however, spinal-cord compression rare)	Technical difficulties with regional
	Kyphoscoliosis	Cardiovascular/respiratory compromise
Hematologic	Bruising after minor trauma although, in most, excessive abnormal bleeding is normally not a problem except for type IV – hematologic complications due to abnormalities in walls of large/small blood vessels	Postoperative hemorrhage Possible contraindication to spinal/epidural Spontaneous rupture of arteries/veins Aneurysms
Gastrointestinal tract	Hiatal hernia, GIT bleeding	Risk of aspiration, anemia
Viscera	Spontaneous rupture of viscera (e.g. uterus/GIT)	Shock – depends on organ involved
CVS	Mitral valve prolapse/regurgitation	Dysrhythmias Bacterial endocarditis prophylaxis
	Proximal aortic dilatation	Rupture

Associated conditions include atrial septal defect, Tetralogy of Fallot, ureteropelvic anomalies and other cardiac anomalies.
IV = intravenous; GIT = gastrointestinal tract; CVS = cardiovascular system

connective tissue in skin, ligaments, tendons, and bone. The exact biochemical abnormality differs in the various subgroups. Mutations occur in the structural genes for type 1 (arthrochalasis EDS), type 3 (vascular EDS), and type 5 collagen (classical EDS) or in genes involved in protein modification of type 1 collagen (kyphoscoliotic and dermatosparaxis EDS).[124] Depending on the type of EDS, these molecular lesions are associated with weakness of the supporting structure of skin, joints, arteries, and visceral organs (see Table 8.18).

Pregnancy and EDS

Numerous reports of complications during pregnancy in women with EDS have appeared in the literature. Unfortunately, many of these reports are anecdotal and the subgroup of EDS not reported. The complications of pregnancy and delivery are clearly related to the subgroup of EDS involved, although publication bias occurs in those patients where complications arise. For women with vascular EDS, (and occasionally in classical EDS), pregnancy may precipitate serious internal complications, including spontaneous rupture of arteries and veins, cardiac valve prolapse, perforation of the colon, aortic dissection, pneumothorax, and uterine rupture.[127,128,129] Early delivery (32 weeks' gestation), or termination prior to 16 weeks' gestation, in type IV EDS has been recommended since this subgroup of women has a high maternal mortality (20%).[129,130] Death occurs from uterine rupture or rupture of a major blood vessel (aorta or vena cava). However, other reports have not described lethal complications from EDS during pregnancy.[127,131,132]

Other potential complications of pregnancy related to EDS include spontaneous abortion, symphysis pubis dysfunction, ruptured viscera (especially gastrointestinal tract), cervical incompetence, uterine prolapse, APH, PROM, lacerations of birth canal, and postpartum hemorrhage (PPH).[130,133,134] Other studies have identified increased fetal risks including prematurity, IUGR, and abnormal presentation.[130,135] The increased risk of prematurity may be related to cervical incompetence or PROM. If the fetus is affected by EDS, one would expect an increased frequency of PROM as the membranes are of fetal origin. Possible reasons for increased malpresentation include increased joint laxity and reduced muscle tone in the fetus affected with EDS.

The treatment of preterm labor in parturients with EDS is controversial but beta-mimetic tocolytics should probably be avoided in patients with type IV EDS following a case report of fatal myocardial infarction and coronary artery dissection.[136] Both vaginal delivery and C/S carry additional risks in these patients. Most clinicians prefer a vaginal birth in the majority of cases, and C/S for those with type IV EDS. It is difficult to provide dogmatic recommendations on the management of delivery due to the protean manifestations of this disease and differences in subgroups of EDS and individual presentations. However, forcep deliveries are considered risky, because bladder and vaginal avulsion have occurred following their use. Vacuum extraction is thought to carry less risk of perineal injury, although there are concerns over an increased risk of cephalohematomas if the fetus is affected by the disease.

EDS and anesthesia

The choice of anesthetic technique will depend on the organs involved, as some types of the disease are innocuous, whereas

others are potentially lethal. A past or family history of visceral/vessel rupture or excessive perioperative bleeding may alert the anesthesiologist to potential ominous complications. It is useful to characterize the type of EDS so that a more accurate prediction of possible problems can be made. Adequate assessment of coagulation status and cardiovascular function is important.

Cardiac problems associated with EDS include valvular disease, congenital heart disease, and conduction defects. In addition, coronary artery disease and myocardial infarction have been described in association with type IV EDS.[137] Price and colleagues[138] reported a case of myocardial ischemia, without prior symptoms, in a 38-year-old woman with type IV EDS, during combined general and regional anesthesia for abdominal aortic aneurysm repair. Evaluation of the EKG may be difficult in these patients due to the associated congenital cardiac abnormalities. However, appropriate investigations should be performed. Cardiac catheterization may be hazardous due to friable arteries, which makes hemorrhage at the entry site a real concern. Stress echocardiogram and thallium scans may be the investigations of choice.

Before induction of anesthesia, patients should have adequate i.v. access, remembering that cannulation of all vessels (arterial and venous) may be complicated by the absence of any sensation of the needle and the cannula traversing the vessel wall. All cannulations and intubations should be performed with care to avoid trauma and hematoma formation, and cannulation sites should be reviewed regularly to avoid extravasation. A history of excessive bleeding is an indication for coagulation evaluation. "Easy bruising" to a variable degree is seen in all subgroups of EDS, and can be explained by capillary fragility. Fragility of medium- and large-sized arteries and veins is also typically seen in the vascular subgroup of EDS and occasionally in the kyphoscoliotic subgroup. Increased bleeding is largely due to a connective tissue defect in the capillary wall, in addition to contributory effects from lack of a tamponade effect from the surrounding tissues. Hematologic studies, including evaluation of clotting factors, platelet aggregation, and bleeding time, are usually normal in EDS patients. One exception is the Hess test, which may be abnormal, indicating increased capillary fragility. Increased bleeding may be compounded by a clotting factor deficiency and platelet abnormalities in some patients.[139] The use of ascorbic acid (a cofactor for crosslinking of collagen fibrils) and deamino-8-D arginine vasopressin (DDAVP) may ameliorate the bleeding tendency in some patients.

Although only a dilemma in type IV patients, one still has to consider the appropriateness of regional anesthesia in each individual patient. However, if there were a history of prior bleeding problems, such as prolonged epistaxis or excessive bleeding after dental extraction, I would personally prefer not to insert an epidural. The risk of epidural hematoma and neurologic complications are likely to be higher due to rupture of vessels from hypertensive responses to painful stimuli. Sudden increases in arterial pressure should be avoided and consideration given to the use of antihypertensive therapy to avoid vessel wall rupture. Obstetric anesthetic implications are discussed in several case reports with the majority of reported cases occurring in the classical and vascular forms of EDS (see Table 8.19).[140,141,142,143,144,145,146]

Table 8.19 Obstetric anesthetic checklist for Ehlers-Danlos syndrome

1. Genetic assessment for severity and type of disease
2. Careful preoperative assessment (particularly cardiac and bleeding tendency)
3. Exclude concomitant coagulopathy
4. Ensure blood available for transfusion if needed
5. Ensure adequate intravenous access
6. Careful cannulations/intubation
7. Careful insertion of spinal/epidural (if not contraindicated)
8. Maintenance of low airway pressure to reduce risk of pneumothorax
9. Avoid hypertension, which may result in the rupture of occult aneurysm
10. Ready availability of methods of uterine contraction (oxytocin, ergotamine, prostaglandin) especially for cesarean section

Although SAB with a small-gauge needle minimizes the risk of bleeding within the epidural space, surgery for C/S in these patients may be protracted due to difficulty in securing hemostasis. Brighouse and Guard[140] reported a case of pregnancy in a woman with EDS type IV, who produced virtually no type III collagen. There were no bleeding problems prior to pregnancy, although abdominal pain in the third trimester was thought to be due to bleeding into the hepatic and splenic capsules. After obtaining a normal coagulation screen and full discussion of risks and benefits of GA versus regional anesthesia, the patient consented to be awake during C/S. A CSE was used and the perioperative period was uncomplicated. The authors argued that a CSE offers a rapid, reliable block with the benefit of prolonged anesthesia should protracted surgery occur.

When GA is undertaken, particular emphasis should be placed on careful, atraumatic intubation (to avoid oral/tracheal trauma and cervical injury), padding of areas vulnerable to pressure effects (to avoid injury to tissues), avoidance of sudden hypertensive episodes (to prevent rupture in major vessels), and maintenance of low airway pressure (spontaneous pneumothorax due to ruptured cysts has been reported).[141]

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) or "brittle bone disease" is a rare inherited connective tissue disorder with a variable clinical spectrum of disease severity. The underlying condition involves osteopenia with primary defects in the protein matrix of bone and other connective tissue. Bone fragility, resulting in an increased risk of fractures, is the hallmark of the disease. The incidence of OI is approximately one per 20 000 births although this may be an underestimation due to the occurrence of milder forms of the disease.[147] Clinical manifestations of OI include excessive bone fragility with predisposition to fracture, short stature, scoliosis, triangular facial configuration (large vault, small jaw), cervical and basilar skull deformities, hearing loss, blue sclerae (decreased collagen content results in pigmented choroid becoming visible),

Table 8.20 Classification of osteogenesis imperfecta

Type	Effects	Inheritence	Manifestations
I	Mild	AD	Variable bone fragility Limited skeletal deformity Stature usually normal Blue sclerae Presenile hearing loss common
II	Lethal	AD/AR	Death in utero or in neonatal period Extremely severe bone fragility Multiple fractures at birth Respiratory failure (severe rib deformity)
III	Progressively deforming	AD/AR	Severe but variable bone fragility Severe deformities of long bones Marked growth retardation and short stature Usually become wheelchair bound White or blue sclerae
IV	Moderate–severely deforming	AD	Variable skeletal deformity and scoliosis Growth retardation less severe than III White sclerae but may be blue in childhood
V	Moderately deforming	AD	Moderate bone fragility Mild to moderate growth retardation White sclera
VI	Moderate–severely deforming	Unknown	Moderate bone fragility Mild to moderate growth retardation White sclera
VII	Moderately deforming	AR	Moderate bone fragility Mild growth retardation White sclera

AD = autosomal dominant; AR = autosomal recessive

dentinogenesis imperfecta, predisposition to bruising, and increased laxity of other connective tissue (skin, ligaments, heart valves). Osteogenesis imperfecta is classified into seven different subgroups, although the major entities are groups I–IV (see Table 8.20).[148] There is significant clinical variability within each subgroup. Type I is the commonest form of the disease and occurs in the majority of reported parturients. Diagnosis is made on clinical grounds and family history. Although definitive laboratory tests are currently unavailable, the analysis of type I collagen genes may be useful. Treatment normally involves a multidisciplinary approach in order to maximize functional capacity, in addition to minimizing fracture rates, deformity, and chronic pain.

Obstetric management

Fertility in patients with type 1 (mild) OI is unaffected by the disease. Musculoskeletal problems, particularly back pain, is common in parturients with OI and may be the result of pregnancy-induced joint laxity.[149] Genetic counseling and prenatal diagnosis should be offered to all affected mothers. Antenatal diagnosis involves a detailed anomaly scan together with biochemical analysis obtained from chorionic villus sampling. Controversy exists regarding optimal delivery mode in these patients. Previous recommendations have been based on limited numbers of case reports. Labor and vaginal delivery is of concern due to a speculated risk of maternal pelvic fractures and fractures in an affected fetus.[150,151] However, Cubert and coworkers[152] reviewed 167 pregnancies in patients with OI and found that C/S did not result in a reduced fracture rate at birth in infants with nonlethal forms of the disease, nor did it prolong survival for those with lethal forms. A high rate of breech presentation was noted and hypothesized to be related to abnormal uterine accommodation of the affected fetus (with disproportionately large head, short extremities, and possible fracture deformities). Individual patients should be evaluated to determine the safest mode of delivery. Cesarean section may be necessary for those with crippling skeletal deformities or severe fetal deformities and absolute cephalopelvic disproportion. However, if vaginal delivery is chosen, trauma from instrumentation should be minimized in order to avoid fetal injury. Case reports have highlighted the risk of uterine rupture and PPH in affected patients.[151,153] Di Lieto and coworkers found a diminished collagen content in the uterine myometrium of a patient with type I OI compared with normal controls.[154] They postulated that the underlying myometrial biochemical modifications were responsible for the increased risk of uterine rupture. To minimize the risk of PPH, an oxytocin infusion should be commenced after delivery to keep the uterus contracted. Osteoporosis accelerated by pregnancy and later by breast feeding may potentially increase the risk of fractures during pregnancy or in the early postpartum period. Calcium and vitamin D supplementation are important preventative measures.

Anesthesia management

There have been several reports describing the successful use of general,[155,156] epidural,[155,157] and spinal[157,158] anesthesia for C/S

Table 8.21 Osteogenesis imperfecta and anesthetic implications

Organ	Dysfunction	Anesthetic/surgical implication
Musculoskeletal	Bone fragility	Care with handling patient, protection of pressure areas during anesthesia
		Care with use of tourniquet
		Avoid use of automated BP devices in severe OI
		Use manual BP devices or invasive monitoring
	Kyphoscoliosis (due to joint hyperdistensibility and vertebral collapse)	Possible neurological deficit (from nerve compression)
		Regionals – technically difficult, unpredictable spread
		Reduced respiratory reserve
	Fragile cervical spine/airway/teeth	Avoidance of trauma to cervical spine/jaw/teeth during intubation, fiberoptic intubation may be necessary
	Cervical instability (odontoid hypoplasia)	Fiberoptic intubation may be necessary
	Chest wall deformities (from previous fractures)	Reduced respiratory reserve
Hematologic	Predisposition to bleeding (possible quantitative/qualitative platelet abnormality, vessel fragility)	Spinal hematoma risk
		Increased risk of perioperative hemorrhage
Thyroid	Hyperthyroidism (40%)	Awareness and correction of thyroid function
Cardiovascular	Aortic incompetence, aortic root widening, mitral valve prolapse	Dysrhythmias, bacterial endocarditis prophylaxis, rupture
Auditory	Deafness	Communication problems
Cellular metabolism	Probable deranged cellular energy metabolism (? hypermetabolic state – hyperthermia during GA)	Intraoperative temperature monitoring, $ETCO_2$ monitoring

BP = blood pressure; OI = osteogenesis imperfecta; GA = general anesthesia

in patients with OI. Early antenatal assessment is important in order that appropriate analgesic and anesthetic methods are discussed. Clinicians should be aware of possible anesthetic and surgical implications of the disease (see Table 8.21). Particular concerns to the anesthesiologist include patient fragility, airway abnormalities, vertebral-column abnormalities, and bleeding predisposition. Clearly, care should be taken when transferring and positioning patients, although degree of patient fragility is variable and some patients have a much greater risk of injury. Tourniquets should be used cautiously and automatic blood-pressure cuffs avoided due to excessive inflation, especially during the initial reading. Manual blood pressure measurement or the use of invasive monitoring may be less traumatic.

Airway examination is important to establish any potential difficulty with intubation. Shortened cervical vertebrae, malformed teeth, micrognathia, and previous fracture deformities have all been described in these patients.[150,155,156] If GA is contemplated, tracheal intubation should be secured with minimal trauma and manipulation to avoid fractures in vulnerable vertebrae, mandible, and teeth. If visualization of the larynx is difficult, the use of a gum elastic bougie or a fiberoptic technique may avoid over-zealous airway manipulation. Although some have expressed concerns regarding maternal fractures secondary to succinylcholine-induced fasciculations, there appears to be little evidence for this. Maternal temperature should be monitored during surgery as hyperthermia and metabolic acidosis have been reported during GA.[159] However OI is not thought to be associated with MH.[155,159]

Regional anesthesia may be challenging due to kyphoscoliosis, short stature, and problems positioning patients with fracture deformities. Hathaway and Solomons[160] found platelet adhesion abnormalities in some patients with OI. Before regional techniques, coagulation and platelet studies should be performed in patients with a history of bleeding tendency. A thromboelastogram may be useful to provide a rapid global assessment of coagulation. Parturients undergoing operative procedure should have blood "typed and saved" or crossmatched prior to surgery. Vogel and colleagues[155] argue that titrated spinal anesthesia may be easier in patients with severe scoliosis, and that incremental spinal anesthesia (via a subarachnoid catheter) avoids unpredictable spread and diminishes the risk of an unintentionally high block in patients with limited respiratory reserve. A titrated epidural or CSE would be suitable alternatives.

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9 DISORDERS OF THE CENTRAL NERVOUS SYSTEM IN PREGNANCY

J. Martinez-Tica and R. B. Vadhera

Introduction

Disorders of the central nervous system (CNS) during pregnancy remain a common cause of maternal morbidity and mortality. Central nervous system disease was responsible for 34 of the 90 indirect causes of death during the 1997–1999 Confidential Enquiry into Maternal Deaths in England and Wales. Intracranial hemorrhage was responsible for 21 of these deaths.[1] Some disease processes pre-date pregnancy, such as epilepsy, Parkinson disease, multiple sclerosis, intracranial lesions, benign intracranial hypertension, or migraine. Other conditions have an increased incidence during pregnancy, for example cerebrovascular disorders, including hemorrhagic or vaso-occlusive strokes.

Few centers have extensive experience treating these CNS disorders, so management is based on isolated case reports, basic principles, and common sense. Maternal vegetative states and brain death situations present medico-legal and ethical dilemmas. Issues important to the care of the parturient with a CNS disorder include:

- the pathophysiology of the lesion
- the impact of pregnancy on the lesion
- impact of medical management, monitoring, and surgery on the fetus
- the potential for aortocaval compression from lead shielding during diagnostic radiological procedures
- gastric aspiration during pregnancy in mentally obtunded patients
- maternal versus fetal priority with respect to surgical plan, timing, and route of delivery
- communication and coordination among the patient, her family, and the medical team (neurologist, neurosurgeon, obstetrician, anesthesiologist, medical consultants, and nursing staff).

Diagnostic tests

A number of intracranial conditions can produce similar signs and symptoms in the parturient (see Table 9.1).[2,3,4,5,6,7,8,9,10] A high index of suspicion for unusual conditions is important because aggressive treatment greatly affects outcome.

Special imaging techniques used for neurological diagnosis include magnetic resonance imaging (MRI), which appears safe for the fetus; computerized tomography (CT) scan, and angiography, which require shielding of the fetus from potentially harmful radiation.[9,10,11] Immobility is required for imaging and, although anesthesia is seldom needed, it may be requested for uncooperative or unstable patients. Possible technical problems include difficulty in positioning the pregnant patient in the scanning apparatus, shielding of the patient and anesthesiologist, and remote access to the patient.

The images from CT scanning are not as detailed as those from MRI, but CT scanning is more readily available and less expensive. Angiography is invasive and can alter neurological function so it is performed ideally in an awake patient. Complications include: vessel occlusion from subintimal vascular dissection from dye, hematoma formation, irritation of cerebral vessels including arterial necrosis, cerebral embolism from hyperosmolar contrast media, as well as sepsis and temporary vasodilation with intense pain. Hyperosmolar solutions produce an osmotic diuresis, which can lead to dehydration, reduced fetal perfusion, and fluid shifts in the fetal brain.[2,10] Myelography can produce headache, confusion, and coma from the irritation of hyperosmolar dyes and from cerebrospinal fluid (CSF) leak following lumbar puncture. The small volume of dye used for a myelogram is unlikely to produce significant osmotic effects in the fetus.

Seizure disorders

A seizure or convulsion is defined as an abrupt alteration in cortical electrical activity evidenced by a change in consciousness or by motor, sensory, or behavioral symptoms. Epilepsy is the term used for recurrent seizures and is the most common neurological disorder in pregnant women (1.1 million women of reproductive age in the United States),[12,13,14] with seizures usually starting in childhood or early life.[15] Eclampsia is the most common cause of seizure during the peripartum period. The neurological manifestations of epileptic seizures are varied and conditions that are commonly confused with epilepsy are syncope, migraine, metabolic and cerebral disorders.[15,16] The types and differential diagnosis of epileptic seizures are shown in Table 9.2. Epilepsy has an impact on many aspects of a woman's health, particularly with respect to reproduction.[17,18] There is a twofold increase in congenital malformations associated with epilepsy and antiepileptic drugs (AED).[12] Epilepsy was responsible for 9 of the 75 indirect causes of maternal deaths in the 1997–1999 Confidential Enquiry in Maternal Deaths.[1]

Management of seizures and pregnancy

The principles of seizure management are to stop the seizure and maintain an unobstructed and protected airway, to ensure oxygenation of both mother and fetus, and prevent aspiration. Eclamptic seizures may be single or multiple, potentially leading to status epilepticus. The definitive treatment of eclampsia is to

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Table 9.1 Symptoms and signs of an intracranial lesion

Symptoms	Signs
• Headaches (if mild may be a warning leak from aneurysm) • Nausea, vomiting • Diplopia, blurred or loss of vision • Photophobia or orbital pain • Epigastric pain • Dizziness • Mental changes • Respiratory distress	• Signs of increased intracranial pressure e.g. hypertension and bradycardia • Nuchal rigidity • Altered consciousness • Focal neurologic signs • Seizures • Ataxia • Bruits • Disseminated intravascular coagulation

Table 9.2 Classification and differential diagnosis of epileptic seizures

Classification	Differential diagnosis
1. Generalized seizures (a) Tonic-clonic seizures (grand mal) (b) Absences (petit mal) (c) Clonic seizures (d) Tonic seizures (e) Bilateral myoclonus (f) Infantile spasms (g) Akinetic seizures 2. Partial seizures (a) With elementary symptoms (b) With complex symptoms (temporal lobe) (c) Partial seizures becoming generalized 3. Status epilepticus	1. Cerebrovascular (a) Stroke (b) Syncope (c) Migraine (d) Eclampsia (e) Mass lesions (f) Infections 2. Drugs (a) Local anesthetic toxicity (b) Intoxication or withdrawal (morphine, cocaine) 3. Metabolic (a) Hypoglycemia (b) Acute intermittent porphyria 4. Cardiovascular (a) Stokes Adam's attacks 5. Obstetric (a) Amniotic fluid embolism (b) Acute fatty liver of pregnancy 6. Others (a) Hysteria

deliver the baby after medical control of the seizure. A report from the Eclampsia Trial Collaborative Group details evidence in favor of the use of magnesium sulfate for routine anticonvulsant management of eclamptic mothers.[19]

Status epilepticus is defined as recurrent seizures without a return to consciousness, or prolonged seizure activity beyond a 30 minute period.[20] The management principles include seizure cessation and prevention, airway management, and identifying a precipitating cause. Maternal and fetal risks are high, including irreversible maternal brain injury and fetal hypoxia, ischemia, bradycardia, and death. In 1982, Teramo and Hiilesmaa reported 29 cases of status epilepticus in labor with the death of 9 mothers and 14 infants.[21] In a recent report from the International Registry of Antiepileptic Drugs in Pregnancy (EURAP) there were 36 cases of status epilepticus with no maternal deaths and only one stillbirth.[22] There is a case report of prolonged generalized tonic-clonic maternal seizures associated with a reassuring fetal heart rate (FHR) pattern and normal fetal acid-base status and oxygenation.[23] Adequate initial treatment with a benzodiazepine, rather than phenytoin, is essential to stop and prevent further seizures. In the first trimester, the benefits of controlling a seizure outweigh the risks from potential teratogenicity associated with some anticonvulsants.[24] Midazolam, given in doses up to 5 mg, produces minimal depression of the fetus. If seizures should occur near delivery, the respiratory depressant effects of higher doses of benzodiazepines can be treated by ventilatory support of the neonate. Tracheal intubation and assisted ventilation for mother may be required and sodium thiopental (STP) helps control the status epilepticus.

Clinical presentation may indicate a need for further investigation and imaging (CT scan and/or MRI) to rule out intracerebral pathology that is amenable to early neurosurgical intervention. Fetal assessment should be performed using ultrasound and cardiotocography to determine the need for obstetric intervention and operative delivery.

Effect of pregnancy on epilepsy

Studies on the influence of pregnancy on the frequency of epileptic seizures have produced varying results, ranging from no change in seizure frequency in 23–50%,[25,26,27] a decrease in frequency in 13–14%,[22,25,26] and an increase in frequency in 17–32% of parturients.[22,25,26] Reasons cited for the differences in the results of these studies are interpretation problems, lack of accurate evaluation of seizure severity and frequency, lack of pregnant controls, and differences in AED treatment before and during pregnancy in some patients.

Hormonal changes during pregnancy seem to affect seizure frequency with estrogen level peaks related to an increase in seizure frequency, while progesterone is associated with anticonvulsant effects. Seizure susceptibility probably correlates best with the estrogen/progesterone ratio.[28] Increased weight (water and sodium), mild respiratory alkalosis, and psychological stress also might play a role.[29]

Plasma concentrations of AED drop during pregnancy. Reasons for this include:

1. decrease in compliance (due to anxiety, nausea and vomiting, and missed doses in labor)
2. decreased absorption and protein binding of the drug
3. increased volume of distribution, hepatic and renal clearance, and body weight.[29]

Folic acid supplements prescribed during pregnancy may also result in lower AED levels. It is the unbound (free) portion of the AED that is biologically active and this level, rather than total drug level, relates to seizure control and to the development of toxicity. Ideally, this level should be established prior to conception and

the medication regimen modified to achieve monotherapy. Free drug levels should be measured monthly during the first and second trimesters and every two weeks in the third trimester. Close monitoring of serum levels after delivery is essential to identify any changes that might require dose adjustment.[25]

Effect of epilepsy on pregnancy

Some studies suggest that there is an increase in complications and adverse outcomes such as hyperemesis, vaginal bleeding, preeclampsia, premature labor, postpartum hemorrhage, and higher obstetric intervention rates in pregnancies of epileptic mothers.[29,30] Other studies found no difference in outcomes when compared to nonepileptic parturients.[31] Antiepileptic drugs are membrane stabilizers and may increase the incidence of vaginal bleeding and duration of labor by reducing the strength of uterine contractions, decreasing coagulation factors and platelet number and function.[32,33]

Effect of epilepsy on the fetus and neonate

The effect of maternal epilepsy on the fetus and neonate may be due to the condition itself, AED use, or a combination of both. Seizures during pregnancy, especially status epilepticus, expose the fetus to the risk of blunt trauma, hypoxia, and acidosis, all of which may produce neurological damage. As seizures increase the risk of fetal and maternal death they require rapid intervention. Treatment of the seizures with intravenous diazepam may cause loss of baseline variability within two minutes of administration. These changes may be interpreted as fetal compromise, leading to an unnecessary urgent delivery. Chronic anticonvulsant therapy is associated with an increase in breech presentation possibly from a lowering of the frequency and strength of fetal limb movements and hence an inhibition of spontaneous version.[33]

The application of a fetal scalp electrode carries a potential risk of scalp bleeding through AED effect on fetal coagulation. Infants born to mothers taking AED can develop potentially life-threatening hemorrhagic disease from vitamin K deficiency, so vitamin K supplements are recommended during the last month of pregnancy.[34] The American Academy of Pediatrics recommends that newborns of epileptic mothers receive vitamin K intramuscularly immediately after delivery[34] and Aminoff recommended that cord blood prothrombin and activated partial thromboplastin times be tested at delivery.[32] Infants with abnormal laboratory values can be treated with fresh frozen plasma or factor concentrates, as appropriate.

All AED are excreted in the breast milk; barbiturates, primidone, ethosuccimide, and the benzodiazepines have the highest concentration in breast milk, while phenytoin and valproate produce lower concentrations. Lethargy and poor feeding in the neonate may necessitate a change to bottle feeding to prevent toxicity.[35] Prolonged use of AED during pregnancy is relatively safe, except during the late third trimester or labor.[36,37] Apnea monitoring and observation of the infant for signs of drug withdrawal are recommended.[35,38]

Table 9.3 Criteria for cesarean section in the epileptic parturient

Elective	Emergency
• Neurologic deficit • Deterioration in third trimester seizure control • Occurrence of seizures with exercise and stress • Unable to cooperate	• Generalized seizure in labor • Threat of fetal asphyxia • Maternal somnolence and lack of cooperation in labor

Infants of epileptic mothers have a twofold increased (to 6%) risk of congenital malformations such as orofacial clefts, congenital heart defects, microcephaly, mental retardation, distal limb hypoplasia, and nail dysplasia. Antiepileptic drugs are implicated in teratogenesis,[39,40] but a contribution from a genetic component related to epilepsy is postulated as children of epileptic fathers have a similar increase in malformations.

Obstetric management

Pregnancies in epileptic mothers are regarded as high risk. Anticonvulsant drug withdrawal or conversion to monotherapy, ideally prior to conception, is the goal along with use of minimal doses of AED for seizure control. This minimizes fetal drug exposure while maintaining maternal seizure control. Obstetric management goals include the abolition of seizures during pregnancy, and a seizure-free delivery of a healthy infant. Counseling the epileptic mother is necessary to ensure compliance with medication, provide information on fetal malformation rates, and possible infant withdrawal symptoms. Breast-feeding is not contraindicated unless the infant shows signs of lethargy.

Anticonvulsant drug levels must be maintained throughout labor and intravenous administration may be necessary due to decreased gastrointestinal absorption. The epileptic parturient is at higher risk for emergency obstetric intervention due to generalized seizures during labor, fetal bradycardia following a grand mal seizure, maternal postictal drowsiness and CNS depression, and loss of FHR variability following rapid intravenous control of seizures. Indications for elective cesarean section (C/S) are shown in Table 9.3.

Anesthetic management

There are many potential interactions among anesthetic drugs and AED as well as anesthetic drugs and epilepsy itself. Phenytoin induces hepatic microsomal enzymes, which affect AED metabolism and enhance the breakdown of opioids, neuromuscular blocking drugs, and volatile anesthetic agents. In turn, this affects drug dosing and production of toxic metabolites (e.g. fluoride ions from sevoflurane).

Some anesthetic agents (e.g. methohexital) are epileptogenic, particularly in the presence of hypocapnia, ketamine, etomidate, and aliphatic phenothiazines. Tricyclic antidepressants lower the seizure threshold. Opioids in high doses cause neuroexcitatory

phenomena in animals but not in humans. Meperidine, and more so its metabolite normeperidine with its long half-life, can cause CNS excitability. Laudanosine, a metabolite of atracurium, can be epileptogenic but this is unlikely in humans. Propofol has been implicated in epileptogenesis, with myoclonic activity and opisthotonos during clinical use, prompting a warning from the United Kingdom Committee on the Safety of Medicine.[41] However, propofol effectively stops seizures in humans and animals,[42] and seizure time is shortened when compared to methohexital for electroconvulsive therapy. Low serum concentrations of amide local anesthetics are anticonvulsant, but at high serum concentrations (e.g. lidocaine 10 μg/ml) they cause convulsions. The action of nondepolarizing neuromuscular blockers may be enhanced by the concomitant use of AEDs, yet with chronic phenytoin use, there may be resistance to pancuronium, but not to atracurium.

The anesthesiologist must also consider the side effects of AED. Phenytoin has multiple side effects: hematological (leukopenia, anemia, agranulocytosis, aplastic anemia) and neurological (peripheral neuropathy). Barbiturates also have similar neurological and hematological (megaloblastic anemia) side effects. Carbamazepine side effects include an antidiuretic hormone (ADH) effect that may induce water retention producing emesis and mental confusion, transient and sometimes persistent leukopenia, and, rarely, agranulocytosis and aplastic anemia.[27]

Anesthetic management during labor

Communication among obstetrician, neurologist, and anesthesiologist is helpful. The prevention and prompt treatment of intrapartum seizures, and provision of effective labor analgesia to reduce anxiety and hyperventilation are the goals of anesthetic care. Evaluation should be carried out with emphasis on the adequacy of seizure control, side effects of therapy, the patient's mental and physical status and proposed obstetric management.

Parenteral opioid analgesia can be used. The dose may require modification to prevent worsening CNS depression in the parturient potentially sedated from anticonvulsants. However, epidural analgesia instituted within accepted guidelines provides superior pain relief and does not depress the CNS. Patients with evidence of a bleeding diathesis require coagulation assessment prior to initiating regional anesthesia. Epidural analgesia is best established incrementally, avoiding high plasma concentrations of local anesthetics, which are epileptogenic.

Anesthetic management during cesarean section

The choice of general or regional anesthesia is determined by a combination of maternal, fetal, and obstetric factors. Postictal and drug-induced somnolence and status epilepticus mandate general anesthesia (GA), recognizing the potential interaction between anesthetic agents and AED, and the need to protect the airway. Regional anesthesia is appropriate for elective C/S in a medically stable patient. As there is a questionable association between spinal anesthesia and potentiation of seizure activity,[29,43] epidural anesthesia may be preferred, remembering that the risk for local anesthetic toxicity is greater. Despite the potential problems facing the pregnant epileptic woman, most will have a stable gestational course and deliver a healthy infant.

Parkinson disease

Parkinson disease (PD, paralysis agitans), is a symptom complex caused by widespread diffuse lesions in the basal ganglia and cerebral cortex, with loss of dopaminergic fibers. Dopamine in basal ganglia normally inhibits extrapyramidal motor neurons from firing. Depletion of dopamine produces unopposed action of neuroexcitatory acetylcholine resulting in diminished inhibition of extrapyramidal motor output. This diminished inhibition leads to signs of tremor at rest, rigidity, bradykinesia, and disturbances of posture. In addition, affected patients may become mentally depressed and develop cognitive and memory deficits that can progress to delirium. Few cases of pregnancy in women with PD have been reported in the literature. Some concerns exist about the consequences of PD on the evolution of pregnancy and labor as well as the potential for teratogenicity[44] and toxicity of antiPD medications.[45,46]

Epidemiology

The annual incidence of PD in North America is 20 per 100 000[47] with a prevalence rate of 190 per 100 000, and a male to female ratio of 3:2. The onset of PD is usually after age 50 (only 5% of patients diagnosed before age 40 in Western countries),[48,49] with a peak incidence in the mid-70s, after which the incidence declines. Familial incidence occurs in 5%. Only 400 women in the United States under age 50 are newly diagnosed as having PD annually, making it rare in women of childbearing age. Only a few cases of PD in pregnant women have been reported.[48] Since there is a significant genetic contribution to the pathogenesis of PD,[50,51] and a trend towards postponing childbearing to a later age with women having babies in their 50s and 60s using assisted reproductive technologies, the number of pregnant women with PD may increase.

Etiology

The precise cause of primary or idiopathic Parkinson disease is unknown. Gene mutations have been identified in early onset and familial cases, but epidemiological studies suggest environmental factors (i.e. pesticide/herbicide exposure) are the dominant cause in most other types of PD.[50,51,52] The observation that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a meperidine analog derived during illicit drug production, produces PD in humans and animals, has resulted in increased interest in the role of toxins, and in the development of an animal model for the study of new treatments.[52,53] Causes of secondary Parkinson disease are shown in Table 9.4.

Pathophysiology

The histopathology findings of PD consist of a selective and severe degeneration of pigmented neurons in the pars compacta of the substantia nigra and a moderate degree of gliosis involving the locus ceruleus and dorsal vagal nucleus, with variable involvement of the nucleus basalis of Mynert.[54] Lewy bodies, concentric, atypical eosinophilic inclusions in the cytoplasm,

Table 9.4 Causes of secondary Parkinson disease

• Drugs	Dopamine receptor antagonists (e.g. antipsychotic and antiemetic drugs)
• Encephalopathy	Posttraumatic pugilist's encephalopathy
• Vascular disease	Small vessel multi-infarct state
• Infections	Postencephalitic
	Prion disease
	HIV
• Miscellaneous	Carbon monoxide intoxication
	Hydrocephalus
	Parathyroid diseases
	Paraneoplastic diseases

HIV = human immunodeficiency virus

although not specific to PD, may be found in the cerebral cortex especially when dementia is present. Similar changes are seen in the basal ganglia. It is thought that the symptoms in patients with PD are due to a disturbance in the regulation of the input to the thalamic nuclei from the cerebellum and the basal ganglia, particularly the globus pallidus, substantia nigra, and other nuclei in the subthalamic region.

Clinical presentation and diagnosis

Parkinson disease is characterized clinically by alternating rest tremor, cogwheel rigidity of muscles, and bradykinesia. Other signs are a mask-like facies, dysarthria, stooped posture, gait abnormalities, slowness and poverty of movements, diminution of associated movements, disturbances of postural control, and autonomic nervous system dysfunction. Diagnosis is generally based on the classical signs of the disorder. Functional imaging single photon emission computed tomography and positron emission tomography improve diagnostic accuracy, especially in patients unresponsive to PD therapy.

Treatment

Treatment of PD is symptomatic and individualized. The available therapeutic measures include nonpharmacologic and pharmacologic treatments, and surgical procedures. Nonpharmacologic interventions (patient education, exercise, and other supportive therapies) are fundamental elements of the overall management of patients with PD and will lead to a comfortable and better lifestyle.

The aim of pharmacological treatment is to restore dopamine balance and reduce acetylcholine-induced neuronal effects. Levodopa, a dopamine agonist, remains the most effective drug in the treatment of PD.[46,55] Levodopa, in combination with carbidopa, an effective inhibitor of the activity of dopa decarboxylase, prevents peripheral breakdown of levodopa in the liver allowing a higher concentration of dopamine to reach the blood–brain barrier. Peripheral side effects (see Table 9.5) are diminished when this combination is used. The sustained release formulation of levodopa-carbidopa (Sinemet® CR) produces constant plasma dopamine levels and a more even clinical response. Levodopa

Table 9.5 Clinical side effects of the administration of levodopa to 60 nonpregnant patients with Parkinson disease[55]

Symptom	No. of patients
Nausea	51
Vomiting	31
Anorexia	19
Postural hypotension	14
Cardiac dysrhythmia	12
Myocardial infarction	1
Psychic manifestations	10
Involuntary movements	37
Laboratory abnormalities	
Leukopenia	5
Positive LE cell preparations	1
Elevated serum urea nitrogen	3
Elevated SGOT	7

LE = lupus erythematosus; SGOT = serum glutamic oxaloacetic >transaminase

should be used with caution during pregnancy as it crosses the placental barrier and may be metabolized in fetal tissues, including the brain and spinal cord. Early fetal exposure to levodopa or dopamine may alter normal fetal neuronal development.[56]

Dopamine agonists (pergolide, pramipexole, ropinirole, cabergoline), now used earlier in the disease management, act directly on the dopamine receptors independent of degenerating dopaminergic neurons. They have a longer half-life than levodopa, provide more sustained striatal stimulation, reduce incidence of motor complications,[57] and are neuroprotective. Catechol-O-methyltransferase (COMT) inhibitors (tolcapone, entacapone) reduce the metabolism of levodopa and are used as adjunctive treatment. Monoamine oxidase (MAO) B inhibitors, selegiline and rasagiline, have been used successfully to increase dopamine levels and may offer some neuro-protection.[58,59] However, these drugs should be avoided in patients taking an antidepressant because of potentially serious CNS toxicity that may represent the serotonin syndrome.[60] There are no reports of these drugs being used in parturients with PD. Amantadine, an antiviral drug, may help rigidity, but its role is limited in pregnancy as its use has been associated with complex fetal cardiovascular lesions.[61] The mode of action is unknown.

Surgery, either stereotactic (thalamotomy, deep brain stimulation) or fetal tissue implantation, is indicated for patients who cannot be satisfactorily managed with medications alone. A parturient is unlikely to undergo surgery while pregnant.

Pregnancy in patients with Parkinson disease

Pregnancy in patients with PD is rare and its precise incidence unknown. At the moment there are insufficient reports of parturients with PD to ascertain the impact of pregnancy on PD and of PD on pregnancy. One report suggests that pregnancy may exacerbate PD and have a long-term negative impact on the course of the illness.[62]

Anesthetic management

Anesthetic management is generally determined by the potential interaction between anesthetic drugs and antiPD medications. Therapy for PD should be initiated before surgery and continued the morning of surgery to decrease drooling, the potential for aspiration, and ventilatory weakness. Reinstituting therapy soon after surgery is crucial as the half-life of levodopa is short. Interruption of therapy for more than 6 to 12 hours can result in severe skeletal muscle rigidity that may interfere with ventilation. It is important to avoid drugs, such as phenothiazines, butyrophenones (droperidol), and perhaps large doses of opioid, that inhibit dopamine release or compete with dopamine at receptors in the basal ganglia. Patients who do not receive levodopa prior to anesthesia are more prone to develop neuroleptic malignant syndrome (NMS), if the anesthetic technique includes antidopaminergic drugs (metoclopramide, droperidol).

An obstructive ventilatory pattern has been observed in one-third of patients with PD.[63] Upper airway dysfunction is common, making patients more prone to retained respiratory secretions, atelectasis, and aspiration. Opioid-induced chest wall rigidity warrants caution. Morphine is known to inhibit dopamine release at a presynaptic level.[64] Alfentanil is known to produce acute dystonic reactions in untreated patients with PD.[65]

In patients treated with levodopa, orthostatic hypotension, cardiac dysrhythmias, and even hypertension can occur during regional, as well as GA.[55,66,67] Rigidity and pulmonary edema have been reported following the use of a combination of fentanyl and droperidol in patients on levodopa.[68] Anesthetizing a patient on selegiline, an MAO B type inhibitor, provides a challenge to the anesthesiologist. The interaction of MAO inhibitors and meperidine may cause profound respiratory depression, hypotension, agitation, excitement, restlessness, hypertension, headache, rigidity, convulsions, hyperpyrexia, and coma.[69]

The use of ketamine is controversial in patients treated with levodopa as it can result in tachycardia and hypertension, or possibly worsen the rigidity due to interaction with the opioid receptor. Despite these concerns, ketamine has been used without difficulty.[70] Nitrous oxide displaces labeled dihydromorphine from opioid receptor sites in the brain so it may precipitate or worsen muscle rigidity in patients who are receiving opioids.[71] There is no absolute contraindication to the use of any particular anesthetic technique; however, one must be aware of potential interaction among dopamine receptor antagonists and opioids, alone or in combination with nitrous oxide. One should avoid metoclopramide because of its antidopaminergic effects. Ondansteron does not appear to worsen the symptoms of PD, unlike dopamine receptor-blocking neuroleptic drugs.[72]

Regional anesthesia

Regional anesthesia for C/S has some obvious advantages over GA: cardiovascular stability, fewer drug interactions, avoids neuromuscular blocking agents and masking of tremors, prevents postoperative nausea, vomiting, and prolonged ventilation.[69] The use of regional analgesia (combined spinal–epidural or epidural) for labor pain is logical and should theoretically reduce leg stiffness, although the epidural placement could be difficult in a rigid parturient with tremors. Intrathecal or epidural morphine might worsen rigidity through a central effect due to its low lipid solubility. Decreased intravascular fluid volume and levodopa treatment may cause hypotension and cardiac dysrhythmias during the induction of neuraxial anesthesia, requiring the aggressive administration of crystalloid or colloid solutions and vasopressors.[55,66,67]

General anesthesia

General anesthesia for C/S might be indicated in patients with severe tremors, or rigidity, or dementia, as these could lead to inadequate surgical conditions or technical difficulty in performing a neuraxial block. The anesthesiologist should always make sure that treatment is optimal.

Aspiration of pharyngeal contents into the trachea may result from dysphagia compounded by excessive salivation. These patients benefit from a rapid sequence induction of anesthesia with appropriate measures to prevent pulmonary aspiration. Cimetidine or ranitidine given an hour prior to induction reduces acid production, and sodium citrate, a nonparticulate antacid, given 20 minutes prior to induction neutralizes the acid present in the stomach. Atropine, as an antisialologue, and ipratropium, as a bronchodilator, can be used perioperatively to reduce pulmonary secretions and, theoretically, relieve any airway obstruction resulting from excessive parasympathetic activity, but they do not prevent aspiration. Atropine is a more logical choice as it crosses the blood–brain barrier and its central effects oppose the prominent cholinergic effects seen in these patients. The anesthesiologist must balance the advantage of rapid onset of neuromuscular blockade with succinylcholine in the dysphagic, pregnant PD patient against a possible hyperkalemic response (a single case report).[73] Muzzi and colleagues failed to substantiate this increase in potassium in nonpregnant patients.[74]

Chest wall rigidity and hypokinesia result in a restrictive pattern of respiratory deficit,[75] and postoperative spasticity may result in airway obstruction requiring ventilation. Involuntary movements (a generalized coarse phasic tremor with tonic rigidity) after GA can be confused with either worsening of PD symptoms or thermoregulatory shivering. Postoperative shivering is mostly transient. In the postoperative period, especially a day after surgery, patients with PD may develop confusion and hallucinations. The precise mechanism of this postoperative confusion is unknown.[76]

Central nervous system neoplasms

Brain tumors occur rarely in young patients and so are uncommon in pregnancy (approximately 90 pregnant patients in the US per year).[7,77] The types of tumor are identical to those seen in nonpregnant women of the same age[77,78] and they may be

benign or malignant, primary or metastatic. The majority are gliomas, followed by meningiomas, acoustic neuromas, and less common tumors such as choriocarcinoma, which is unique to pregnancy. Spinal tumors are rare, representing 12% of CNS neoplasms during pregnancy. Prognosis varies according to the type of tumor. Gliomas arise from astrocytes and oligodendrocytes and vary in degree of malignancy from slow growing to highly anaplastic, producing tissue damage and a mass effect. Meningiomas are benign tumors that grow slowly from the membranes covering brain and spinal cord, ultimately producing a mass effect. Acoustic neuromas are slow-growing, benign tumors arising from the vestibular portion of the eighth nerve and are often seen in patients with neurofibromatosis. Pituitary tumors are benign and slow growing, producing a variety of hormones (growth hormone, adrenocorticotrophic hormone, prolactin), and visual-field defects from compression of the optic chiasm. Choriocarcinoma, an invasive, malignant tumor of trophoblastic origin, is prone to metastasis and may develop after a molar pregnancy, abortion, ectopic gestation, or term pregnancy. Metastatic brain lesions are found in 3–20% at the time of initial diagnosis of choriocarcinoma.[79,80] In the spinal cord, hemangiomas and meningiomas are the most common tumors, producing symptoms related to compression of surrounding structures.

Clinical presentation and diagnosis

Nonspecific symptoms from brain tumors include constant headache and persistent nausea and vomiting secondary to increased intracranial pressure (ICP). In the pregnant patient these must be differentiated from common headache and morning sickness. Most patients demonstrate lateralizing signs, including hemiparesis, sensory loss, visual-field defects, and aphasia. Seizures, focal or generalized (with or without a focal onset), are also common with low-grade gliomas and meningiomas and must be differentiated from other causes. Patients with spinal-cord tumors causing compression can present with painless weakness and numbness of the legs, followed by paralysis and loss of sphincter function. Magnetic resonance imaging scanning is used to define mass lesions and is preferred over CT, which is less sensitive and requires shielding.

Neurosurgical management

Low-grade gliomas are slow growing and usually are surgically removed electively after delivery. High-grade gliomas are surgically removed without delay with concomitant radiotherapy and chemotherapy. Since these treatments pose a significant risk to the fetus, decisions about treatment must be individualized. In the case of a slow-growing meningioma, 30% can be completely resected while the remainder requires subtotal resection or radiation. Pituitary tumors are treated by trans-sphenoidal resection or, in the case of prolactinomas, bromocriptine therapy. For choriocarcinoma, radiation and chemotherapy are used and surgery is reserved for those with a single metastatic lesion to the brain or those requiring decompression. Anticonvulsants and corticosteroids are used, when indicated. Spinal hemangiomas and meningiomas with rapidly progressing symptoms are treated with decompression laminectomy, but vertebral resection and intradural surgery may be required.

Effect of pregnancy and obstetric management

Pregnancy may cause enlargement of meningiomas and acoustic neuromas possibly from fluid retention, increased blood volume, and engorgement of blood vessels.[10] The hormones of pregnancy may facilitate tumor growth, since 90% of meningiomas and some gliomas have progesterone receptors. Maternal hypertension, increases in ICP, and seizure activity must be controlled throughout pregnancy and especially during labor. Method of delivery for a parturient with brain tumor remains controversial, and is likely to be influenced by the presence of high ICP. Many obstetricians prefer to deliver patients with brain tumors by C/S if there is increased ICP;[81] however, similar maternal and fetal outcomes can be achieved with pain-free labor and assisted vaginal delivery.[82] Tewari *et al.* described eight parturients with malignant brain tumors diagnosed during pregnancy; all had a neurologic crisis between 27 and 32 weeks. Six of these patients were delivered emergently, and four of the patients died.[83] If the symptoms could be controlled pharmacologically these authors recommended C/S in the early third trimester followed immediately by neurosurgical intervention.

Anesthetic management

The anesthetic management is guided by the presence or absence of symptoms and signs of elevated blood pressure (BP) and ICP.[84] Pain during labor and pushing can increase ICP, while good pain control by regional analgesia helps minimize any fluctuations. This analgesic benefit has to be balanced against the risk of brain-stem herniation following an inadvertent dural puncture.[85] Epidural injection of local anesthetics increases epidural-space pressure possibly causing a worsening of symptoms.[86] Wakeling described exacerbation of CNS symptoms, dizziness, paresthesiae in both hands, and transient rigid immobility, after an epidural in a parturient with an unknown large cerebello-pontine angle tumor and obstructive hydrocephalus.[87]

For C/S in a parturient with raised ICP, preinduction measurement and control of ICP and BP is mandatory. An arterial line and ventriculostomy with an ICP pressure transducer assist in controlling the response to tracheal intubation, as therapy (antihypertensive drugs, hyperventilation, and mannitol) can be titrated to maintain homeostasis. Anesthesia for neurosurgical intervention during pregnancy is discussed later in the chapter.

Central nervous system infection

Infection of the brain and spinal cord can become organized into abscesses, which produce symptoms similar to other mass lesions.[88,89,90,91,92] Anesthetic considerations are the same as those for brain tumors and other space-occupying lesions.

Table 9.6 Types of strokes during pregnancy or puerperium in 15 women at Parkland Memorial Hospital from 1984–1990[24]

Hemorrhagic strokes (6)	
Saccular aneurysm	1
Arteriovenous malformation	1
Hypertensive	3
Unknown	1
Ischemic strokes (9)	
Arterial thrombosis	2
Arterial embolism	3
Venous thrombosis	2
Vasculitis	1
Moyamoya disease	1

Stroke

A stroke is defined as a syndrome of acute neurological injury following rupture or occlusion of vessels in the CNS. Cerebral vessels can rupture from trauma or inherent weakness, and can be occluded from within by thrombosis or embolus or externally by a mass lesion (see Table 9.6).[2,3,4,5,6,7,11,24,93] The incidence of maternal stroke secondary to a bleeding cerebral aneurysm is 1:6000[3] to 1: 30 000[24] pregnancies with a 20% mortality and a 50% incidence of permanent neurological sequelae.[3] The risk of stroke from cerebral infarction and intracerebral hemorrhage (ICH) is increased in the six weeks after delivery but not during pregnancy.[8]

Central nervous system hemorrhage

Intracranial hemorrhage has an incidence of 1 to 5 per 10 000 pregnancies and is either subarachnoid (SAH), bleeding into the subarachnoid space from lesions near the surface of the brain, or intracerebral, bleeding into the brain parenchyma.[11] The pathophysiologic effects of intracranial hemorrhage result from a compressive mass effect and irritation from blood and its breakdown products. Intracerebral structures are relatively noncompressible, so even a small hemorrhage can result in significant anatomic distortion, a large increase in ICP, and a reduction in cerebral perfusion.

Subarachnoid hemorrhage

Subarachnoid hemorrhage occurs in 0.01 to 0.05% of pregnancies[2,5,9,10,11,24,94,95,96,97] and is associated with either a saccular (Berry) aneurysm in 77% parturients, or an arteriovenous malformations (AVM) in 23% parturients, with an overall mortality of 5–12%.[24] Intracranial aneurysms result from a weakening of the internal elastic lamina of large arteries at the base of the brain, usually at a bifurcation. Often the vessel wall is thinnest at the dome of the aneurysm, and it ruptures into the subarachnoid space of the basal cisterns, the subdural space, or directly into the underlying brain parenchyma. Aneurysms can leak spontaneously. Precipitating factors for rupture include: bleeding disorders, hypertension, and cocaine abuse.[98] Arteriovenous malformations can occur in most parts of the brain and spinal cord and are abnormal, thin-walled communications between the arterial and venous system, which are prone to rupture.[99] A large malformation can produce an arteriovenous shunt sufficient to raise the cardiac output.

Clinical presentation and diagnosis

Unruptured aneurysms are usually asymptomatic while large aneurysms can produce headache and focal neurologic signs depending on their location. Subarachnoid hemorrhage may produce severe headache, photophobia, nausea and vomiting, periorbital pain, nuchal rigidity, and a positive Kernig sign.[100] Throbbing headache, changing sensorium, and seizures are more characteristic of hemorrhage into the brain parenchyma from an AVM. Vasospasm is seen more commonly in patients with a bleeding aneurysm than a bleeding AVM.[6,101] When a major hemorrhage occurs, the following can happen.

- Intracranial pressure approaches the mean arterial pressure, decreasing cerebral perfusion and resulting in a transient loss of consciousness.
- A severe headache occurs either before loss of consciousness or upon awakening.
- Rarely, acute vascular spasm leads to additional focal neurologic signs with stupor and impaired autoregulation.
- The electrocardiogram (EKG) often shows ST and T wave changes similar to those of myocardial ischemia, along with a prolonged QRS complex, increased QT interval, and prominent peaked or inverted T waves. The cause of these EKG changes has been debated, but there is evidence that structural myocardial lesions may occur, possibly secondary to intense sympathetic activity.[11,95] These lesions are usually not associated with an elevated creatine kinase. The EKG changes generally do not correlate with the extent of cardiac injury. The grade of SAH may correlate with wall motion abnormalities on echocardiography.

After a bleed the following complications can occur.

- Rebleeding in 10–30% of patients during the first three weeks following aneurysmal rupture, with a mortality of 50–60% with each rebleed.
- Vasospasm occurs in 35% of patients 4 to 11 days following SAH, leading to further neurological deterioration.
- Hydrocephalus occurs in 15–20% of patients following SAH, from blood and cellular exudate blocking efflux of CSF. This is manifested by a gradual decrease in the level of consciousness.
- Cerebral edema or hyponatremia from inappropriate ADH (SIADH) secretion can be seen.

Subarachnoid hemorrhage is life threatening and surgery can be life saving, therefore a CT scan, MRI, and possibly lumbar puncture (presence of blood/xanthocromia) should be carried out promptly. Angiography is performed to define the lesion for surgical intervention.

Neurosurgical management

Controversy exists over the optimal time to operate on parturients suffering from SAH.[2,9,10,24,93] Early surgery reduces the incidence

of vasospasm and rebleeding and seems to be associated with lower maternal and fetal mortality.[24] However, the patient may be unstable (worsening neurological status, poorly controlled hypertension) and surgery itself may induce vasospasm. Surgery may or may not be of benefit after an AVM bleed.[24,102] The decision to operate is based primarily on neurosurgical considerations, although advances in the maintenance of normotension, normovolemia, hemodilution, and improved treatment of vasospasm favor early clipping of aneurysms to prevent rebleeding.[95,96,97,103]

Effect of pregnancy and obstetric management

In the past it was thought that aneurysms, but not AVM, were at increased risk of bleeding with advancing gestational age.[100] The current opinion is that both aneurysms and AVM tend to bleed more as pregnancy advances, possibly due to the hemodynamic and hormonal changes of pregnancy.[24] This explanation does not account for the rarity of intracranial hemorrhage during labor and delivery when hemodynamic changes are maximal. Hemorrhage resulting from AVM does not cluster during any particular trimester, and the incidence in subsequent pregnancies is increased.[99] The incidence and mortality from intracranial hemorrhage in parturients are similar to that of the general population.[24,99]

If an aneurysm has been clipped, there is no increased risk for vaginal delivery.[104] If the aneurysm is untreated, the risk of intrapartum rebleeding is greatest if the initial bleed occurred during the third trimester. An uncorrected AVM is more likely to bleed during labor and delivery than an aneurysm. Some authors recommend elective C/S at 38 weeks' gestation,[102,104,105] but others have found no advantage over vaginal delivery.[24] Currently, most would recommend operative delivery with an unclipped and previously ruptured aneurysm.

A combined C/S and neurosurgical procedure can be undertaken when indicated.[2,10,93,106,107,108,109] If urgent, the neurosurgical procedure is carried out prior to delivery.[110,111] In patients with obstetrical reasons for expeditious delivery, the neurosurgical procedure may be performed remote from delivery.

Anesthetic management (see Table 9.7)[95,110,111,112,113]

Aneurysm clipping may be delayed in unstable patients.[95,112] It is important to minimize transmural pressure (mean arterial pressure–intracranial pressure) across the aneurysm wall to minimize the risk of rebleeding.

General anesthetic considerations for C/S are the same as those for other neurosurgical procedures. Epidural anesthesia has been used for C/S[114,115] and for vaginal delivery[116,117,118] in patients with a medically managed intracranial aneurysm. One report has described the successful use of either epidural or GA for C/S in three women with AV malformations.[119]

Table 9.7 Anesthetic goals for clipping a cerebral aneurysm in the parturient

- Minimize transmural pressure (mean arterial pressure–intracranial pressure)[a]
  Prevent hypertension and maintain normal mean arterial and intracranial pressure
- Maintain normal oxygen saturation and normocarbia[b]
- Maintain appropriate analgesia, muscle relaxation, and amnesia
- Close monitoring of volume status
- Mild hypothermia (36–35°C) may be considered to reduce cerebral metabolic rate – brain protection (prevent shivering with muscle relaxation)
- Vasospasm may require nimodipine treatment and triple "H" therapy, i.e. hypervolemia, hypertension, and hemodilution
- Head elevation
- Left uterine displacement to minimize aortocaval compression
- Early awakening

[a] It is imperative that intracranial pressure not be lowered until the dura mater is opened to minimize changes in the transcranial pressure gradient on the aneurysm wall and associated bleeding.
[b] Hypocarbia potentially reduces placental perfusion.

Intracerebral hemorrhage

Hemorrhage into the brain parenchyma of pregnant patients is rare, is often secondary to hypertensive disorders,[5,10,120] and remains the most common cause of death in an eclamptic patient.[121,122] One report noted three strokes of hypertensive etiology in 90 000 parturients studied.[3] Two of these parturients had underlying chronic hypertension, and all three patients had residual neurological deficits.[3] The incidence due to less common etiologies is unknown.

Severe preeclampsia causes arterial vasospasm, multifocal petechial hemorrhages, and may be accompanied by SAH.[123] Hypertensive ICH typically occurs in the basal ganglia, thalamus, cerebellum, or pons. Intracerebral hemorrhage can also accompany SAH caused by aneurysms or AVM. The risk of ICH in pregnancy is increased with metastatic choriocarcinoma, Moyamoya disease, Kaposi sarcoma, occult carotid-cavernous fistula, bleeding diatheses, and cocaine abuse.[5]

Clinical presentation and diagnosis

Pregnant patients with ICH present with an abrupt onset of a neurologic deficit referable to the site of the hemorrhage, commonly accompanied by headache, nausea, and vomiting. A noncontrast CT scan is the most sensitive test to diagnose acute ICH, but contrast CT scan, MRI scan, or angiography may be needed to exclude a structural etiology. A bleeding disorder should be ruled out. It is important to differentiate ICH from SAH, because treatment differs greatly.

Neurosurgical management

Intracerebral hemorrhage is often not amenable to surgical correction and has a poor prognosis.[124] Treatment is supportive, with control of BP and ICP. Surgery is reserved for life-threatening elevations of ICP, brain-stem herniation, and evacuation of an expanding hematoma that is well defined.

Effect of pregnancy and obstetric management

Obstetric considerations should determine the mode and timing of delivery. Cardiovascular effects of pain and pushing during

labor and delivery may elevate the ICP and BP during preeclampsia, worsening the ICH. Cesarean section offers no advantage in limiting hemodynamic stress over painless vaginal delivery modified with limited pushing during the second stage, but a perimortem C/S may be required. If a hematoma is present, surgical evacuation may be required, with delivery at a later date.

Anesthetic management

Blood pressure must be controlled prior to surgery, but may be difficult to manage in the hypertensive or preeclamptic parturient. These patients often have a low intravascular volume, which increases the risk of severe hypotension and decreased placental perfusion following anesthetic induction.[10] In these cases, optimal fluid replacement is guided by the use of a central venous pressure or Swan-Ganz catheter. Diuretics such as mannitol and furosemide may be used intraoperatively to reduce brain bulk and facilitate surface exposure. Mannitol increases the fetal osmolality significantly and should be used with caution.[125] Intracranial pressure should also be controlled preoperatively.

Regional anesthesia is generally preferred for hypertensive patients, if coagulation status is normal, as it avoids the hypertensive response to intubation and reduces the risk of regurgitation and pulmonary aspiration. If GA is used, BP is controlled with labetalol or sodium nitroprusside, using an arterial line to assess the response to therapy on a beat-to-beat basis. Preeclamptic patients are observed for postpartum convulsions and managed with magnesium sulfate and/or benzodiazepines.

Spinal hematoma

Bleeding into the spinal area can occur spontaneously or, rarely, following regional anesthesia.[126,127,128,129,130] Patients who are treated with anticoagulants may, rarely, develop a spontaneous bleed.[131] The incidence of neurologic dysfunction resulting from hemorrhagic complications associated with central neural blockade is estimated to be less than 1 in 150 000 epidural and less than 1 in 220 000 spinal anesthetics.[132] Risk factors include traumatic needle/catheter placement, sustained anticoagulation with an indwelling neuraxial catheter, and catheter removal during therapeutic levels of anticoagulation.[133] Thrombocytopenia accompanying preeclampsia is also thought to be a risk factor.[134,135] Considering the vascularity of the epidural space, it is surprising that clinically detectable hematomas are not seen more often following regional anesthesia. A spinal hematoma can develop rapidly or insidiously and is usually related to arterial bleeding. The patient may complain of severe burning back pain that progresses to motor dysfunction (usually bilateral) and the loss of bowel and bladder function. It is important to follow the American Society of Regional Anesthesia (ASRA) guidelines before and after regional anesthesia, if a parturient takes anticoagulants.[134]

Pain from an epidural hematoma must be differentiated from the pain and motor dysfunction associated with a prolapsed intervertebral disc and other neurological complications of pregnancy, such as meralgia paresthetica.[136] Neurological examination usually will differentiate these lesions based on their single nerve or nerve root distribution.

A spinal hematoma is a medical emergency as nerve compression and ischemia will result in permanent damage – often in less than six hours after the onset of symptoms. An MRI is diagnostic. The only effective treatment is emergency decompression if a hematoma mass-lesion is found.[129] Spontaneous partial recovery occurs rarely.[137,138]

Central nervous system ischemia

Cerebral ischemia

Ischemic stroke is uncommon in women of childbearing age and results from occlusion of the cerebral circulation (venous or arterial) due to a variety of causes. In one report, ischemic strokes were observed in 9 of 90 000 pregnancies.[3] In another report, cerebral thrombosis was present in 1 of 29 000 pregnancies.[139] Kittner *et al.*[8] showed that the relative risk for cerebral infarction during pregnancy was 0.7 (adjusted for age and race) compared with a relative risk of 8.7 in the first six weeks after delivery.

Cerebral venous thrombosis (CVT) occurs during the early postpartum period in most cases. Underlying precipitating factors for cerebral venous thrombosis are shown in Table 9.8. Thrombosis of the sagittal sinus with extension to the cortical veins is not uncommon. Sagittal sinus thrombosis blocks reuptake of CSF and produces intracranial hypertension. Cortical vein thrombosis produces focal cerebral ischemia and edema, and, when extensive, bland or hemorrhagic infarction. For arterial occlusion, specific etiologies in parturients are similar to those in other young adults (see Table 9.9).[5]

Clinical presentation and diagnosis

Cerebral venous thrombosis presents with a gradual onset of focal deficits, while arterial emboli produce a more sudden onset of symptoms. Cerebral venous thrombosis usually presents with a progressive headache, nausea and vomiting, blurred or double vision, and altered sensorium secondary to increased ICP. Cerebral venous thrombosis may be mistaken for eclampsia (or be associated with it) or aneurysm rupture. Cortical vein occlusion produces focal or generalized seizures and lateralizing signs that affect the proximal extremities.

Table 9.8 Precipitating factors for cerebral venous thrombosis

Excessive blood loss during delivery
Infection
Hyperviscosity syndromes
Sickle cell disease
Malignancy
Polycythemia rubra vera
Paroxysmal nocturnal hemoglobinuria
Dehydration
Procoagulation syndromes
Antiphospholipid antibody syndrome
Deficiency of protein C and S
Arteriovenous malformation
Endothelial injury
Venous statsis

Table 9.9 Etiology of arterial occlusion

Type	Association (risk factors)
• Arteriopathies	• Premature atherosclerosis (smoking, hypertension, diabetes, hypercholesterolemia, homocystinuria, radiation to the neck, and a family history of arteriosclerosis) • Arterial dissection (inflamed cerebral arteries)
• Hematological	• Sickle cell crises (ischemic injury to the vessel wall) • Systemic lupus erythematosus (SLE) • Thrombotic thrombocytopenic purpura (TTP)
• Embolism	• Embolism from artificial valves, mitral valve prolapse, atrial fibrillation, and subacute bacterial endocarditis • Others: air, fat, and amniotic fluid embolism, as well as paradoxical emboli from veins in the presence of a patent foramen ovale
• Idiopathic	• No cause found in 25%
• Miscellaneous	• Migraine related • Drug induced (cocaine, heroin, and amphetamines)

Ischemic strokes must be differentiated from hemorrhagic or structural lesions, which may be surgically treatable. Recurrence of stroke is common so it is important to diagnose and treat any underlying medical condition. The diagnosis is based on clinical information, laboratory investigations (including coagulation studies), CT, MRI, and angiography where indicated. Treatment of patients with CVT is supportive with administration of antiseizure medication. These patients usually recover rapidly and spontaneously without neurological sequelae.[140,141,142]

Effect of pregnancy and obstetrical management

The incidence of cerebral infarction is increased 13-fold during pregnancy[139] due to the hypercoagulable state of pregnancy and hormonal changes.[143] Obstetric considerations should determine the mode of delivery.

Treatment

Treatment is based on underlying etiology. During an acute thrombotic episode the parturient might be treated with anticoagulants. Urokinase, intravenous tissue plasminogen activator (TPA), and heparin (either low molecular weight [LMWH] or unfractionated) have all been used successfully in parturients.[111,144] Low molecular weight heparin is used increasingly as it has a predictable anticoagulant effect, less frequent dosing, and requires minimal monitoring. These medications may be changed, after an acute episode, to subcutaneous heparin and aspirin to minimize recurrence and converted to warfarin, aspirin, or clopidogrel after the delivery.[145] Surgery may be needed if there is hemorrhagic transformation of the infarct with mass effect and increased ICP, or for ventriculoperitoneal shunting and placement of ICP monitors.

Anesthetic management

During labor, hypertension and elevated ICP are avoided by careful induction of epidural analgesia/anesthesia and avoidance of pushing in the second stage with assisted vaginal delivery. Systemic hypotension may reduce cerebral perfusion and blood flow to an already compromised, injured area. In patients receiving anticoagulants, precautions outlined in the ASRA guidelines should be followed.[134] Reversal of therapeutic anticoagulation may be required if a regional anesthetic technique is considered safe. For C/S, the risk of a dural puncture from an epidural needle must be weighed against the risks of exacerbating hypertension with tracheal intubation in women with elevated ICP. Avoid hyperventilation during GA as it may compromise cerebral and uterine blood flow. Postoperatively, the patient must be observed for recurrence or extension of local thrombus or increased ICP.

Spinal-cord ischemia

Anterior spinal artery syndrome has been reported rarely in parturients suffering severe and/or prolonged hypotension and presents with painless paraplegia secondary to spinal-cord ischemia.[146] Spinal-cord ischemia is rarely reversible. See Chapter 10.

Benign intracranial hypertension

Benign intracranial hypertension or "pseudotumor cerebri"[147] is defined as an increase in ICP without a demonstrable etiology and is a diagnosis of exclusion. Benign intracranial hypertension is thought to occur in 1:1000 pregnancies, with a 30% recurrence rate in subsequent pregnancies.[148,149] It has been reported to be more common in obese women of childbearing age, suggesting a hormonal etiology,[147] but some evidence suggests that it may not be more common in pregnancy.[93] It may occur after chronic use of specific medications such as tetracycline. Over production and/or under absorption of CSF are proposed mechanisms. The disease is usually benign, but increased ICP can lead to optic nerve atrophy and blindness.[150]

Clinical presentation and diagnosis

Headache, stiff neck, papilledema and visual disturbances occur from increased ICP, but consciousness is not affected. Cerebrospinal fluid pressure is elevated to above 200 mmH_2O, CSF composition is normal, and imaging studies are normal.

Neurosurgical management

Treatment consists of serial lumbar punctures to drain CSF. Brain-stem herniation usually does not occur, because the increase in ICP is uniformly distributed throughout the CNS.

However, two cases of cerebellar tonsillar herniation have been reported after diagnostic lumbar puncture in nonpregnant patients with this syndrome.[151] These patients presented with severe headache, neck pain, and focal neurologic signs. If the patient experiences progressive loss of vision then optic nerve decompression[148,152] or a lumboperitoneal shunt is required.[150]

Effect of pregnancy and obstetric management

Some authors suggest that symptoms worsen during pregnancy,[149] suggesting a hormonal etiology, but Digre and colleagues[153] found that visual loss occurred with the same frequency in pregnant and nonpregnant patients. Obstetric complications occurred more frequently in the controls, so obstetric management should not be significantly altered by this disorder.[153] Treatment of pseudotumor cerebri during pregnancy is the same as for nonpregnant patients, except that calorie restriction and diuretic use (acetazolamide) are contraindicated. The condition usually resolves postpartum.

Anesthetic management

General anesthesia may be required for placement of a lumboperitoneal shunt or replacement of a blocked shunt. The usual precautions for nonobstetric surgery during pregnancy apply.[154] Regional analgesia for labor and delivery has been described and deemed to be safe,[148,155] but caution is warranted as cerebellar tonsillar herniation has been described after diagnostic lumbar puncture in two nonpregnant patients (see earlier).[151] If a lumboperitoneal shunt is in place, GA may be preferable for C/S as the impact of the shunt on extension of spinal anesthesia is unknown. With an unknown CSF volume or pressure it might be difficult to adjust the dose of local anesthetic. However, spinal anesthesia has been successfully used in a patient who likely had low CSF volume and pressure from a continuous CSF leak at the base of the skull.[156] As parturients with benign intracranial hypertension often undergo a diagnostic spinal tap they have the potential to develop a postdural puncture headache and an epidural blood patch may be considered. Blood placed in the epidural space may increase ICP through compression of the dura mater, so slow injection may be warranted.

Hydrocephalus with shunt

Hydrocephalus is an abnormal accumulation of CSF in the brain. The CSF is often under increased pressure, which can compress and damage the brain. Hydrocephalus can be due to many causes (see Table 9.10) and may require ventriculoperitoneal or ventriculoatrial shunts to relieve raised ICP. The incidence of pregnant patients with CSF shunts is unknown, but successful treatment of congenital hydrocephalus in childhood has translated into more women with ventricular shunts reaching childbearing age.[157,158,159]

Clinical presentation and diagnosis

In patients with shunts, hydrocephalus may recur due to shunt malfunction, commonly due to infection or mechanical damage. A physical examination and a CT/MRI scan should be performed to rule out other causes. If the scan is normal, a lumbar puncture can exclude other processes, such as benign intracranial hypertension.

Table 9.10 Causes of hydrocephalus and increased intracranial pressure

Hydrocephalus	Increased intracranial pressure

• Congential aqueductal stenosis
• Non-inherited
  ○ Dandy-Walker anomaly
• Acquired, secondary to:
  ○ subarachnoid hemorrhage
  ○ infection
  ○ tumor
• Inherited neural tube defect
• Arnold-Chiari malformation
	• Traumatic brain injury
	• Pseudotumor cerebri
	• Arnold-Chiari malformations
	• Brain tumor or other mass lesion
	• Hydrocephalus
	• Lyme disease
	• Severe hypertension

Neurosurgical management

Shunts are placed or replaced when the patient develops signs of raised ICP. Ventriculoperitoneal shunts are the most resistant to infection, and are used commonly. Prophylactic antibiotics are recommended to prevent infection of the shunt during revision.

Effect of pregnancy and obstetrical management

Pregnancy may precipitate symptoms of hydrocephalus in a patient with a previously well-functioning shunt or in a woman without a preexisting shunt,[157] but these are unlikely to increase obstetric complications.[160] In 59% of pregnant patients with a preexisting shunt pregnancy increased ICP resulting in symptoms of severe headache.[157] If ICP is normal there are no specific obstetric considerations. However, prophylactic antibiotics will reduce the risk of shunt infection, especially if the peritoneum is entered during C/S or tubal ligation.

Anesthetic management

General anesthesia is used for shunt placement, with emphasis on controlling ICP (see Table 9.11), BP, and maintaining adequate anesthetic depth. Regional anesthesia has been used for vaginal birth as well as C/S in these patients,[158,161,162] although there is concern about the dose required and potential spillage of the local anesthetic into the peritoneal cavity. Kaul *et al.* reported that the duration of local anesthetic inadvertently injected into the subarachnoid space in a parturient with a lumboperitoneal shunt was shorter than normal. They postulated that this might have been caused by washout of the anesthetic into the peritoneal cavity and felt that spinal anesthesia may not be practical in parturients with lumboperitoneal shunts.[163]

Increased intracranial pressure

One of the most damaging aspects of brain trauma and various other conditions is elevated ICP that can cause a reduction in cerebral perfusion. An elevated ICP correlates directly with poor

Table 9.11 Methods of reducing intracranial pressure

Method	Effect	Caution
Diuretics		
Mannitol (0.25–1.0 g/kg)	Hyperosmolar diuresis ↓ brain water, volume of brain, and ICP	Acts only if BBB intact Can increase ICP, if BBB not intact Transient vasodilation, hence increases ICP May precipitate pulmonary edema Can cause fetal dehydration, and fetal brain shift and hemorrhage
Furosemide (1 mg/kg)	Systemic diuresis ↓ CSF production ↓ ICP	Fetal dehydration Moderate doses usually safe
• Corticosteroids dexamethasone	↓ elevated ICP by restoring integrity of the BBB, allowing diuretics to work more effectively May take hours to days to have that effect	Short term: minimal effects on the fetus[94] Long-term therapy may cause hyperglycemia, gastrointestinal bleeding, electrolyte disturbances, infection, and fetal adrenal suppression[24]
• Acute hyperventilation (normal pCO_2 is 32–34 mmHg in term parturient)	Cerebral vasoconstriction ↓ CBF ↓ ICP by 4%/1 mmHg reduction in pCO_2 Moderate ventilation to $PaCO_2$ of 25–30 not harmful to fetus	↓ fetal perfusion secondary to uterine vasoconstriction Shifts O_2 dissociation curve to left, reducing fetal O_2 delivery Effect limited by renal compensation over prolonged hyperventilation
• CSF drainage		
Ventriculostomy Lumbar spinal catheter	Can monitor ICP Control ICP precisely	Additional risk of infection requires antibiotic cover
• Posture		Increases the probability of pulmonary air emboli
Head up Neutral, if possible	Improves venous drainage Reduces ICP	Use precordial Doppler Neck rotation may decrease venous return thereby increasing ICP

BBB = Blood Brain Barrier; ICP = intracranial pressure; CSF = cerebrospinal fluid; CBF = cerebral blood flow
Arterial pressure and ICP should be measured at brain level.

neurological outcome. The symptoms of raised ICP are headache, nausea and vomiting, ataxia, papilledema, visual disturbances, and decreasing levels of consciousness. An acute increase in ICP due to an expanding intracranial lesion, can lead to brain-stem herniation, but loss of consciousness may occur before signs of herniation are seen. Signs and symptoms of brain-stem herniation include: decreasing level of consciousness, lateralizing neurologic signs ("unilateral blown pupil", abducens nerve palsy), sudden changes in BP and pulse (Cushing triad), vomiting, irregular respiration, respiratory collapse (Cheyne-Stokes respiration), and seizures. The differential diagnosis includes acute obstetric disasters, such as amniotic fluid embolism. In the parturient, increased ICP can occur secondary to uterine contractions (resulting in a 200–300 ml autotransfusion) and increases in arterial and venous pressure from pain and the Valsalva maneuver.

Monitoring and control of intracranial pressure

The normal ICP is <15 mmHg.[164] An ICP that remains between 30–35 mmHg for prolonged periods may prove fatal. Intracranial pressure should not be allowed to go above 40 mmHg for even brief periods. The rapid progression of this life-threatening emergency makes immediate surgical intervention the first priority and diagnostic CT or MRI scan a secondary issue. Immediate treatment may involve cardiopulmonary resuscitation, tracheal intubation, and hyperventilation. If the ICP exceeds 25 mmHg, it must be reduced to maintain cerebral perfusion. Periods of risk for increased ICP during pregnancy include: laryngoscopy and intubation, extubation, straining during labor and delivery, and postpartum when the uterine autotransfusion leads to an acute increase in blood volume. A number of methods may be used to control ICP during the perioperative period (see Table 9.11).

Anesthesia for delivery in a parturient with raised ICP

To prevent increases in ICP, labor should be as pain free as possible and the second stage should be shortened by using oxytocin, and instrumental delivery. Monitor BP, oxygen saturation, and ICP (if indicated) throughout labor and in the immediate postpartum period when the cardiovascular changes are maximal.

The decision concerning pain relief must be individualized. Systemic analgesics may depress respiration and increase ICP. A paracervical block provides adequate anesthesia during the first stage, but can compromise the fetus. Pudendal block with local infiltration may be used for the second stage and assisted delivery.

Segmental lumbar epidural anesthesia reduces the pain of labor, limits straining, and helps with pain-free assisted vaginal delivery. In the parturient with increased ICP there is the risk of a "wet-tap" during epidural placement that could cause a sudden leakage of CSF and theoretically lead to brain-stem herniation. Therefore, the anesthetic technique should be selected with these complications in mind. If there is concern about increased ICP, a ventriculostomy can be used to measure ICP and withdraw CSF, if needed. The ability to withdraw CSF should be checked prior to attempting the epidural. An epidural bolt measures ICP, but cannot be used to withdraw CSF. Placement of a lumbar epidural catheter by the most experienced person available reduces the chance of a dural puncture. A caudal approach may reduce, but not eliminate, the possibility of dural puncture, but it is rarely used. Spinal anesthesia should not be used if the ICP is elevated.

Cesarean delivery may be required for obstetric indications. General anesthesia allows a simultaneous neurosurgical procedure.[106,107] For the patient with a possibly difficult airway, the effects of respiratory obstruction and straining on BP and ICP during a fiberoptic intubation must be considered.[165,166] If lumbar epidural anesthesia is selected, the same considerations apply as for vaginal delivery. Some authors have used epidural[115] and spinal[167] anesthesia for C/S in patients with intracranial lesions. It can be argued that spinal anesthesia with a small, pencil-point spinal needle is unlikely to cause a significant CSF leak in patients with raised ICP[167] but this remains controversial. If labor occurs when neurosurgery is planned, an emergency C/S followed immediately by an intracranial procedure may be performed under GA.

Considerations for neurosurgery during pregnancy

Monitoring

It is important to monitor oxygen saturation, EKG, end-tidal CO_2, FHR, direct arterial and central venous pressures, ICP, and, occasionally, electroencephalogram (EEG) and sensory-evoked potentials.

Intravenous fluid management and blood pressure control

In unconscious patients and those with intracranial lesions, fluid and electrolyte balance can be problematic as a result of decreased fluid intake, vomiting, and the use of hyperosmolar dyes for angiography. Severe fluid restriction produces minimal reduction in ICP because fluid loss is isotonic, but it can cause a reduction in uteroplacental perfusion. Intravenous fluid loading is sometimes used to maintain BP, cerebral perfusion, and fetal perfusion. Hypotension and hypovolemia can exacerbate intracranial vasospasm[112,113] so judicious hypervolemia, while measuring ICP and FHR, is appropriate. Control of BP throughout the perioperative period is important for maintaining ICP, cerebral perfusion, and fetal perfusion.

Vasopressors and antihypertensives should be selected with the fetus in mind. Although ephedrine benefits fetal perfusion by constricting capacitance and resistance vessels, and increasing myocardial contractility, it may increase shear stress on sensitive intracranial vessels and so must be used cautiously. Most recent clinical evidence suggests that phenylephrine, which increases afterload, is safe for the fetus.[22,168,169] However, in large doses, phenylephrine has the potential to reduce uteroplacental perfusion secondary to its alpha-adrenergic effect on uterine vasculature. Antihypertensive agents such as labetalol, hydralazine, nifedipine, nitroglycerin, and brief infusions of nitroprusside are safe for the fetus in normal doses.[22,170,171] The lack of placental autoregulation means that placental perfusion is directly related to maternal mean blood pressure. The effect of volume expanders, diuretics, vasopressors, or vasodilators must be considered in terms of their impact on cerebral perfusion, maternal end-organ perfusion, and placental perfusion. Clearly, in some situations what is best for maternal homeostasis may be detrimental to the fetus.

Brain protection

Various methods may be used to minimize further neurological damage in the perioperative period by reducing continuing damage to surrounding tissues. Many of these methods are experimental and the effects on the fetus are unknown.

Anesthetic management for neurosurgery during pregnancy

Emphasis is placed on selection of surgical procedures with the welfare of the parturient in mind, since the well-being of the mother determines fetal outcome. Method of delivery is often selected based on obstetric considerations. The impact of preoperative therapy and anesthetic intervention on the mother and fetus should be considered when formulating an anesthetic plan. Urgent surgical intervention is required only in the most severe cases (massive trauma, epidural hematoma, brain-stem herniation). Major considerations include the neurological status (including level of consciousness, ICP), diagnosis, cardiorespiratory compromise, and status of the fetus. Maternal condition should be as stable as possible before proceeding to surgery and appropriate monitors should be in place.

Preanesthetic and anesthetic goals include control of BP, cerebral blood flow, and ICP, prevention of aspiration, and maintenance of fetal perfusion. Anesthetic management for a neurosurgical procedure during pregnancy is similar to that for a nonpregnant patient with the following exceptions: surgery is best deferred until the second trimester, the well-being of the fetus is assessed throughout surgery by monitoring FHR, and left uterine displacement is ensured to avoid aortocaval compression especially during late third trimester. After preoxygenation and induction, cricoid pressure is applied until the endotracheal tube is secured. These precautions also apply when intubating the trachea of a comatose, unstable patient, remote from surgery.[4] Succinylcholine (100–120 mg) remains the most reliable neuromuscular blocker for intubation. The resulting fasciculations may temporarily increase ICP and BP, but this is of little clinical consequence. If succinylcholine is contraindicated and the woman has an adequate airway, rocuronium may be given in a dose 0.6–1.0 mg/kg.

Most anesthetic drugs are safe for the fetus,[172] but second trimester surgery negates concerns about teratogenesis. Premature

labor can occur following any nonobstetric surgery. The risk is much greater following abdominal or pelvic than neurosurgery. Early detection with continuous monitoring for uterine contractions and treatment is important.

Induced hypotension is used occasionally to control bleeding during clipping of intracerebral aneurysms,[110,111,173] but it may have adverse effects on the fetus.[10] If induced hypotension is used, it should be limited in depth and duration, adjusting the mean BP upwards if the FHR pattern becomes unfavorable (e.g. sudden fetal tachycardia or decelerations). Improvements in FHR pattern have been described after correcting hypoxemia,[174] or by increasing flow during cardiopulmonary bypass.[175]

Cerebral trauma

A variety of traumatic head injuries have been reported in the parturient,[6,172] and the incidence of traumatic brain injury in the USA is in the range of 152–430 per 100 000/year. The mortality rate is 30 per 100 000/year with a large number suffering permanent disabilities. Approximately 7% of pregnant women will suffer a bodily injury, with motor vehicle accidents and alcohol ingestion as major contributory factors. Prompt diagnosis and management can be life saving.

Head injury may be classified as closed or open (penetrating). Closed injuries may be diffuse or focal. Diffuse injury, often caused by acceleration–deceleration, ranges from simple concussion (transient loss of consciousness) to severe axonal disruption. Focal injuries include subdural hematoma, epidural hematoma, and cerebral contusion. A subdural hematoma occurs when the bridging veins between the brain and the dural venous sinuses are disrupted as a result of an acceleration injury. Epidural hematomas are caused by direct skull trauma leading to rupture of the meningeal arteries, which are embedded in the grooves of the skull. Cerebral contusions are heterogeneous areas of necrosis, infarction, hemorrhage, or edema. Coup contusions result from deformation of the skull at the point of impact, and contracoup contusions result from deceleration of the brain against the skull. Intracerebral hematomas result from depressed skull fractures, penetrating wounds, or acceleration–deceleration injuries. Missiles produce a variety of injuries. In addition to neurologic damage, major long-term complications of cerebral trauma include epilepsy and hydrocephalus.

Clinical presentation and diagnosis

Concussion injury ranges from temporary unconsciousness, disorientation, amnesia, dizziness, and disequilibrium to coma and death. Acute subdural hematomas present as rapidly expanding mass lesions, with hemiparesis, pupillary abnormalities, or both. Cerebral epidural hematomas can present with immediate loss of consciousness, followed by a lucid interval, later followed by neurologic symptoms such as headache and increased lethargy. Some may not experience unconsciousness until some time after the injury. Symptoms of subarachnoid hemorrhage can also occur. Contusions, hematomas, and missile injuries produce a variety of localized and diffuse signs and symptoms.

History, physical examination, laboratory tests (including coagulation studies, blood gases), and other imaging studies are useful to establish the extent of injury to the brain and other systems. If neuroradiologic examination is needed, it should be performed promptly. The fetus can usually be shielded, and radiation of the fetus should be considered a minor risk in life-saving situations.

Neurosurgical management

Management includes control of BP, ICP, ventilation, maternal cerebral perfusion, and fetal perfusion. Surgical intervention is indicated for subdural and epidural hematomas, for intracerebral hematomas associated with a mass effect and/or neurological deterioration, for symptomatic ICP greater than 25 mmHg that is not responding to treatment, depressed skull fractures, hydrocephalus, and to place ICP monitors.

Effect of pregnancy and obstetric management

The incidence and morbidity of cerebral trauma in pregnant women are similar to a matched nonpregnant population.[6] In the presence of severe head trauma, injuries to other organ systems must be ruled out, especially the vulnerable gravid uterus, with the potential for uterine rupture, placental separation, and fetal trauma. A discussion of fetal injury is beyond the scope of this chapter. Injury may precipitate premature labor, and since the obtunded patient cannot indicate that she is in labor, fetal monitoring should be initiated and early delivery anticipated. Method of delivery is based on obstetric considerations.

Anesthetic management

Anesthetic management for neurosurgery is similar to that in the nonpregnant patient, bearing in mind those factors important in dealing with nonobstetric surgery during pregnancy.[154] Exposure to teratogens is of concern, but judicious use of commonly used agents is safe in the absence of hypoxemia, acidemia, and hypercarbia. Anesthetic management for delivery is similar to that in pregnant patients suffering from intracranial hemorrhage (see earlier).

The comatose parturient

Coma is the term used to describe unconsciousness from which a person cannot be aroused. A multitude of etiologies exist, all of which may complicate pregnancy and pose great threat to the mother and her fetus (see Table 9.12). Further along the continuum of CNS deficits are the entities of chronic vegetative state and brain death, which pose medical, ethical, and legal dilemmas, especially when considered in the context of a viable pregnancy.

The immediate treatment goals are prevention of further nervous system damage, rapid correction of hypotension, hypoglycemia, hypoxia, hypercapnia and hyperthermia, and control of seizures. The unconscious parturient may require endotracheal intubation and ventilation to protect the airway from aspiration

Table 9.12 Differential diagnosis of coma

Intracranial	Extracranial
1. Vascular Hemorrhage (subarachnoid) Cerebral infarction (embolus, thrombus, or vasculitis) 2. Tumor Hemorrhage Edema 3. Abscess Hemorrhage Edema 4. Infection Meningitis Encephalitis 5. Trauma Edema Hemorrhage (subdural, extradural, or intracerebral) 6. Epilepsy Postictal Status epilepticus	1. Hypotension Hemorrhage Myocardial infarction Septic shock 2. Hypertension Encephalopathy: eclampsia 3. Metabolic Endocrine Hepatic Renal Hypoxia Hypercarbia 4. Drugs/toxins 5. Physical Hypothermia Electrocution

pneumonitis and to correct hypoventilation. Fetal viability should be assessed after maternal stabilization.

History and a thorough clinical examination with neurological and laboratory evaluation will indicate the need for neuroimaging techniques such as CT scanning, MRI, MR angiography, and conventional angiography. An accurate diagnosis allows for development of an individualized management plan, utilizing a multidisciplinary approach. Specific treatment is directed towards pathology leading to coma. Long-term management goals are adequate nutrition and avoiding complications like infections, bed sores, and contractures.

In general, neurosurgical considerations dictate management in the case of life-threatening intracranial hemorrhage, while obstetric decisions are based on fetal viability. In mothers with Hunt and Hess Grades IV and V postsubarachnoid hemorrhage, supportive intensive care is preferred to early repair.[176] Brain tumors, especially meningiomas, may increase in size during pregnancy leading to possible coma. The outcome for the fetus is determined by the individual circumstances. If the fetus is viable and neurosurgical intervention mandatory, C/S before craniotomy may be indicated.[177] Steroids may be administered to enhance fetal lung maturity.

Hypoglycemic coma, not associated with insulin therapy, is rare in pregnancy, chiefly because pregnancy confers insulin resistance. Insulinoma may be diagnosed with simultaneous determination of plasma glucose, insulin, and C-peptide levels in the fasting state. In one case report, treatment consisted of a 50% glucose infusion and supportive care until the pancreatic tumor was excised postpartum.[178] Prolonged maternal hypoglycemia may cause precipitous fetal compromise. During short-term maternal hypoglycemia the FHR pattern changes, and following treatment it returns to a fully-reactive trace and normal baseline.[179] Another rare cause of hypoglycemia in pregnancy is lymphocytic hypophysitis, which causes anterior pituitary deficiency in the absence of a radiographically identifiable pituitary tumor or neurofibroma. In one report, treatment consisted of an initial 50% glucose infusion with good response, followed by thyroxine and cortisol replacement once the diagnosis of panhypopituitarism was established.[180]

Management of maternal vegetative state and brain death

A chronic vegetative state is defined as a subacute or chronic condition that sometimes occurs after brain injury and consists of a return of wakefulness accompanied by an apparent total lack of cognitive function. The vital functions of respiration, blood pressure, and thermal regulation are retained and may be subject to periods of overactivity.

Brain death results from total cessation of cerebral blood flow at a time when cardiorespiratory function is preserved by artificial life support. It is a diagnosis made according to strict criteria. Brain stem and hypothalamic centers do not function, resulting in a lack of spontaneous respiration, hypotension, hypothermia, and panhypopituitarism, including diabetes insipidus with concomitant treatment problems.

Advances in intensive care, life-support systems, and neonatology make possible the continuation of pregnancy in the vegetative or brain-dead parturient. Moral and ethical problems abound regarding withdrawal of support from the vegetative mother postpartum. No rules can be laid down as each case must be assessed individually with liaison among family members, legal advisors, ethicists, and the multidisciplinary care team. Beware of medicolegal implications of issues regarding consent and cessation of treatment, planned C/S, and perimortem C/S.

The management of a pregnant patient with irreversible anoxic brain damage and in a persistent vegetative state from 14 weeks' gestation until delivery at 34 weeks' by C/S is described by Hill *et al.*[181] Management issues in this case included: seizure control, respiratory support ranging from tracheobronchial toilet to mechanical ventilation, hemodynamic monitoring and cardiovascular support, nutritional support, maintenance of normothermia, treatment of infection, physiotherapy, thromboembolism prophylaxis, and fetal monitoring with serial ultrasound examinations, biophysical profile scoring, and lung-maturity assessment. The authors stressed a team approach to decision-making with each case assessed individually with regard to the likelihood of maternal survival and fetal prognosis with continued life support.[181] Betamethasone may be administered to stimulate fetal lung maturation, if indicated. The timing of delivery, often by classical C/S, is determined by maternal condition and fetal maturity.

Case reports in the literature outline scenarios and management issues. Fulminant subacute sclerosing panencephalitis is a rare cause of rapid neurological deterioration culminating in a vegetative state. Pregnancy as a state of natural immunosuppression was suggested as the trigger for the delayed onset and

fulminant course of this measles virus-associated, progressive, fatal disease in two pregnant women. One mother developed the disease postpartum while the other became ill at week 14 and stuporous two weeks later. Supportive and intensive obstetric care was provided and C/S was performed after the onset of spontaneous labor at 33 weeks' gestation.[182]

Syndromes

Sturge-Weber disease/syndrome

Sturge-Weber syndrome, also known as Krabbe-Weber-Dimitry disease, is a neurocutaneous syndrome, which is probably more common than would be concluded from the relatively small number of cases recorded in the literature. The cardinal features of this disease are a localized atrophy and calcification of the cerebral cortex with an associated intracranial venous malformation (angiomatosis) and an ipsilateral port-wine colored facial nevus, usually located in the ophthalmic and maxillary distribution of the trigeminal nerve. Any portion of the cerebral cortex may be affected by the atrophic process, but the occipital and parietal regions are most commonly involved. Vascular changes are found also in the leptomeninges, pituitary, thymus, lung, spleen, and lymph nodes.[183,184,185] Altered blood vessel fibronectin expression in Sturge-Weber syndrome could contribute to abnormal vascular structure and function.[186]

Clinical manifestations may range from localized, superficial skin lesions to extensive systemic involvement. It is possible for the combination of a port-wine facial nevus and localized cortical atrophy to exist without clinical symptoms, but in the majority of cases convulsions are present from infancy. Mental retardation, contralateral hemiplegia, or hemianopia without cerebral infarction are present in a high percentage of cases.[187] Ipsilateral exophthalmia, glaucoma, buphthalmos and angiomas of the retina, optic atrophy, and dilated vessels in the sclera may also be present. The combination of Sturge-Weber disease with other phakomatoses has often been noted. In most cases, the angiomas and hypertrophy coincide in an arm or leg, as in Klippel-Trenaunay syndrome and on one side of the face as in Sturge-Weber syndrome, but exceptions and dissociated forms have been noted.[185] Klippel-Trenaunay syndrome (see Chapter 3) is a rare congenital malformation that may include: port-wine stain usually on one limb, soft tissue and bony hypertrophy (excessive growth of the soft tissue and/or bones), venous malformations (varicose veins), and lymphatic abnormalities (lymphedema). Fused toes or fingers, or extra toes or fingers, may be present. Complications may include cellulitis, venous thrombosis, or pulmonary embolism. Bleeding may occur, often as a result of a rectal or vaginal capillary tumor. There is no associated CNS atrophy. Anesthetic implications from peripheral venous malformations are similar to Sturge-Weber Syndrome without any CNS signs and symptoms.

Sturge-Weber disease can be diagnosed without difficulty from the clinical syndrome. The presence of the cortical lesion can be demonstrated in the majority of cases by the appearance of characteristic shadows in the x-ray. The lesions in the occipital and parietal lobes are usually more calcified than those in the frontal lobe. Minimal cerebral involvement is difficult to detect and can only be diagnosed by angiography or contrast-enhanced CT scan. It is recommended that any parturient with a port-wine nevus in the ocular trigeminal nerve distribution have an MRI with contrast to rule out an ipsilateral intracranial vascular malformation, especially if a seizure disorder is present.[184,188]

Any patient who presents with complaints of seizure disorder, facial nevus, ocular manifestations, or an intracranial vascular malformation should be evaluated early in pregnancy and managed by a multidisciplinary team. The treatment of patients with Sturge-Weber disease is essentially symptomatic. Control of seizures follows similar principles as outlined earlier, and requires optimal control with anticonvulsive drugs. Subarachnoid and subdural hemorrhage may occur but are uncommon. Heart failure occurs rarely and is due to shunting through the intracranial angiomas. Recurrent thrombotic episodes producing gradual loss of function may require use of antiplatelet agents.[184,189,190] Many patients will have had AV malformations or other anomalies treated surgically. Photodynamic therapy or external beam radiation therapy has been recommended, but there is no evidence that they are of any benefit.[191,192] Hemispherectomy may be of benefit to control seizures.[193]

Table 9.13 Clinical manifestations and anesthetic concerns in a parturient with Sturge-Weber syndrome

Clinical manifestations	Anesthetic concerns
• Seizures • Contralateral hemiparesis • Contralateral hemianopia • Headaches • Developmental delay • Mental retardation • Glaucoma • Choroidal hemangioma • Strokes • Bilateral cerebral involvement	• Control of seizures • ↑ ICP • ↑ IOP • Difficult intubation from airway hemangiomas • Uncontrolled hemorrhage, from rupture of hemangiomas • Uncommon Subarachnoid/subdural hemorrhage Heart failure from shunting Recurrent thrombotic episodes

ICP = intracranial pressure; IOP = intraocular pressure

Anesthetic management

The signs and symptoms (i.e. location of the nevus, symptomatology, and vascular anomaly) and careful evaluation for associated anomalies determine the choice of anesthetic technique. Anesthesia should be carefully planned to avoid any trauma to the hemangiomatous lesions and to prevent any rise in intraocular or intracranial pressure (see Table 9.13).[185] Anesthetic concerns for the epileptic parturient have been discussed earlier.

Special attention needs to be paid to intubation and extubation. Difficulties with tracheal intubation may occur due to angiomas of lip, oral cavity, tongue, larynx, and trachea.[194] Uncontrolled hemorrhage may result from perforation of vascular lesions. Tracheal intubation therefore should be performed as atraumatically as possible, with soft, nonstylleted, well-lubricated endotracheal tubes. Care during tracheobronchial suction is mandatory.

Sudden increases in BP must be avoided during induction and intubation due to potential rupture of the malformations. Ocular manifestations require avoiding anesthetic agents that may increase intraocular pressure. Straining, bucking, and obstructed airways during induction or emergence may increase intraocular, as well as intracranial, pressure.[185] An increase in ICP can result in intracranial hemorrhage from associated vascular malformations.

Regional anesthesia (spinal or epidural) is safe and logical in the majority of cases, especially when localized superficial skin lesions exist without clinical symptoms. Lumbar epidural analgesia with a low concentration of local anesthetic provides a continuous stable anesthetic level during first stage, which can be augmented for assisted vaginal delivery during second stage of labor. With the more dilute local anesthetic solutions (e.g. bupivacaine 0.0625% with fentanyl 2–2.5 ug/ml) there is minimal motor block, hence pelvic muscle tone is maintained, possibly decreasing the incidence of fetal malposition. If an epidural is not in place spinal anesthesia (saddle block) may be administered to facilitate an assisted vaginal delivery.

Two concerns with the use of epidural block are the potential for increased ICP caused by the injection of anesthetic drugs into the epidural space, and the catastrophic consequences of sudden CSF leakage from an inadvertent dural puncture in the presence of an intracranial lesion. Slow continued leakage of CSF after the needle has been withdrawn may be responsible for some cases of delayed neurological deterioration. The presence of an epidural catheter adjacent to the dural hole, as in the case in the combined spinal–epidural (CSE) technique, may be associated with less CSF leakage as reflected by an extraordinarily low incidence of post-dural puncture headache.[195]

Preexisting neurological disease of the spinal cord or peripheral nerves is a relative contraindication to neuraxial block, but there are circumstances when major conduction blocks are in the best interest of the mother and her fetus. These patients might have a spinal AVM, which is unlikely to cause any problems during the regional procedure itself providing it is performed below the caudal end of spinal cord. Epidural or spinal anesthesia is preferred for C/S if time permits, and providing ICP is normal and the patient agrees. General anesthesia is an option in cases of extreme urgency, where there is increased ICP, where the patient is uncooperative, or for obstetric considerations. Epidural anesthesia may also be used in combination with GA for C/S in order to minimize perioperative hypertension and improve postoperative analgesia.

Arnold-Chiari malformation

Adult onset Arnold-Chiari malformation (ACM) is primarily characterized by herniation of the cerebellar tonsils through the foramen magnum into the upper cervical spinal canal. Classification and clinical manifestations of ACM are shown in Table 9.14. Symptoms of ACMs are due to high ICP from obstruction of CSF flow from fourth ventricle or pressure effects of displacement, or entrapment of cranial nerves, resulting in occipital headache, shoulder and arm pain with cutaneous dysesthesia, visual disturbances, intermittent vertigo, and ataxia. Symptoms become worse with head movement and coughing. Neuronal impairment of the medulla can cause sleep apnea, respiratory failure, and death.[196] Rarely, syncopal episodes have been described and attributed to either compression of the midbrain ascending reticular system, or vascular compromise (vertebrobasilar artery compression, hypotension).[197]

Syringomyelia, a slow onset progressive myelopathy characterized by cystic degeneration within the spinal cord, is documented in 50% of ACM patients.[196] Symptoms of syringomyelia include skeletal muscle weakness, wasting, areflexia with or without thoracic scoliosis, and severe neurological deficits. Women with Chiari I malformation with or without syringomyelia are of particular concern because of the potential risk of

Table 9.14 Classification and clinical manifestation of Arnold-Chiari malformation

Classification	Clinical manifestations
Chiari I:	
Herniation of medulla & cerebellar tonsils 4th ventricle in normal position	High ICP from obstruction of CSF flow from 4th ventricle Occipital headache – worse by coughing, strain, and head movement Vomiting, difficulty swallowing, and hoarseness Arm and neck pain, visual disturbances, intermittent vertigo, and ataxia
Chiari II:	
Herniation of medulla, tonsils, and vermis 4th ventricle at foramen magnum Myelomeningocele Aqueductal stenosis with hydrocephalus	Paralysis of the legs, muscle wasting, ataxia, areflexia, and mental impairment High ICP and hydrocephalus symptoms
Chiari III:	
Further herniation 4th ventricle below foramen magnum Encephalocele or myelomeningocele Syrinx	Neuronal impairment of medulla can cause breathing abnormality, swallowing difficulty, sleep apnea, and respiratory failure Scoliosis Progressive myelopathy

ICP = intracranial pressure; CSF = cerebrospinal fluid

Table 9.15 Anesthetic concerns in parturients with Arnold-Chiari malformation

↑ Intracranial pressure	Worsening symptoms and possibly brainstem herniation
	During pushing
	Inadvertent dural puncture
	General anesthesia: at induction, intubation, and extubation
	During epidural injection
Scoliosis/ syringomyelia	Technical difficulty
	Spread of local anesthetics (LA)
	Possibility of enhanced LA neurotoxicity
	Damage to spinal cord: if higher space chosen for regional anesthesia
Meningomyelocele	Nerve/spinal cord damage
	Space may be shallower
Lower motor neuron lesion	Possibility of hyperkalemia with succinylcholine
	Prolonged nondepolarizing neuromuscular block
Autonomic dysfunction	Hypotension
	In hypovolemic patients with an increase in intrathoracic pressure
	Vasodilation caused by spinal or epidural anesthesia
Shunts	Leakage of drug into peritoneal cavity
	Shorter action of LA
	Difficult to calculate dose of spinal LA

increased ICP during pregnancy and delivery.[198] Involvement of the autonomic nervous system is not uncommon.[199]

Treatment of patients with an ACM includes posterior fossa decompression surgery, ranging from freeing adhesions, enlarging the foramen magnum, suboccipital craniectomy, laminectomy of C1, and dural patch grafting, to dural splitting of the craniocervical junction.[200]

Seven pregnant patients suffering with an ACM, with and without syringomyelia, reported no significant increase or recurrence of ACM-related symptoms during delivery or postpartum.[198]

Anesthetic management

Selection of anesthesia might be largely dependent upon the presence and severity of symptoms and a history of any decompression surgery. Anesthetic concerns are shown in Table 9.15. Successful use of spinal anesthesia,[201,202] epidural anesthesia,[198,203] as well as GA[199] for C/S in parturients with Arnold-Chiari type I malformation have been described. Agusti described GA for C/S in a woman with ACM where the only complication was an exaggerated response to atracurium.[199] The reason GA was selected was to avoid spinal manipulation, which might increase ICP or reduce intraspinal pressure, causing a deterioration of neurological symptoms.[199] In these five reports there were no surgical complications or worsening of neurological symptoms.

Spinocerebellar ataxia (Friedreich ataxia)

Spinocerebellar ataxia (SCA) is a collection of diseases in which slow CNS degenerative changes are chiefly localized in the spinal cord and the cerebellum; all of them are clinically characterized by progressive ataxia. Friedreich ataxia is a familial and hereditary disease with degenerative changes chiefly localized to the dorsal half of the spinal cord and the cerebellum. The impact of Friedreich ataxia on pregnancy and the obstetric/anesthetic management of women with this condition is detailed in Chapter 8.

Summary and future directions

Many of the lesions discussed in this chapter are uncommon, so it is important that there is prompt reporting of individual cases. Advances in neurosurgical, obstetric, and anesthetic management have resulted in a recent trend to treat the parturient aggressively for her neurological condition, as the welfare of the fetus ultimately depends on the health of the mother. Appropriate monitoring, rational, preemptive control of physiological variables, communication, a coordinated team approach, and timely intervention based on predetermined triage priorities are essential to optimal management.

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10 SPINAL CORD DISORDERS

Roanne Preston

Introduction

Patients with spinal cord injuries and spina bifida are not commonly encountered in the obstetrical population, but their numbers will increase in the future as a result of improved surgical techniques and rehabilitation therapy. Also, women with degenerative spinal cord diseases such as spinal muscular atrophy, and amyotrophic lateral sclerosis are surviving to child-bearing age and choosing to become pregnant despite the risks. Unusual diseases of the spinal cord such as tethered cord, syringomyelia and postpolio syndrome are also known to occur in pregnant women.

Spinal cord injury

The incidence of spinal cord injury (SCI) is 25–30 per million of population in North America, or 10 000 new cases per year in the USA. Most victims are young, and in Canada 20% of them are female.[1,2,3] Advances in both acute and rehabilitation care have led to improved outcomes resulting in higher levels of independent function after SCI. Rehabilitation emphasizes integration back into society and cord-injured patients are encouraged to work, establish relationships, and have families.

Pregnancy in SCI patients is no longer rare; a 1999 survey looked at 472 women with SCI, all at least one year post injury.[4] Fourteen percent became pregnant after their injury, and in 60% it was their first pregnancy. The average time to pregnancy following SCI is 4 to 13 years, but the average age at pregnancy and time interval since injury have decreased in the last few years.[5,6,7] The first successful pregnancy in a quadriplegic was reported in 1953.[8] Most reports since then involve chronic SCI, although there are some reports on management of the pregnant patient with acute SCI.[9,10,11,12,13,14]

The acute spinal cord-injured pregnant patient

Pregnant women constitute less than 1% of total acute admissions to trauma centers.[9] Acute SCI incurred during pregnancy is uncommon,[9] and often is associated with a high incidence of miscarriage, stillbirth, and fetal abnormalities (14/45 in a 1970 review).[10,11] Second trimester pregnancies have the worst outcomes, partly due to uterine trauma with placental abruption or direct fetal trauma.[10,11,12,13,14] The primary survey of the pregnant trauma patient with a viable fetus (>24 weeks' gestation), should include fetal heart rate monitoring. This may provide useful data about maternal hemodynamic status.[3,15,16] High dose steroid therapy is not contraindicated.[3,16] If the fetus remains viable, there are two approaches to the management of the mother with SCI. One approach is enforced bed rest with spinal immobilization until the fetus is viable, followed by cesarean section (C/S) and spinal stabilization at one surgery. However, the risks of prolonged bed rest, including thromboembolism, and acquired secondary neurological injury during this period, favor early surgical intervention. The risks of early intervention include a possible impact on the fetus of prolonged surgery in the prone position, and hemodynamic instability secondary to spinal shock. Due to the small number of cases reported, the actual risk of preterm labor is unknown.[5,17,18] Unstable thoracolumbar fractures invariably require early surgical stabilization as a body brace may compromise the growing fetus.

The initial phase of acute SCI, lasting three to six weeks, is known as spinal shock and is due to the sudden interruption of suprasegmental descending neurons, which normally keep spinal motor neurons in a continuous state of readiness.[19] Spinal shock is characterized by flaccid paralysis below the level of the lesion and loss of all sensory modalities, temperature regulation, and spinal reflexes (tendon and autonomic). Cardiovascular effects include hypotension (may be severe), bradycardia (with high thoracic lesions), and dysrhythmias. Fetal heart monitoring during spinal shock provides information about the fetus and maternal hemodynamic status.[20] Due to loss of vasomotor tone, the extremities lose heat rapidly if exposed, and develop dependent edema. There may be a prolonged period of paralytic ileus. Cervical lesions at C2–4 usually mandate ventilatory support for a prolonged or permanent period, while lower cervical lesions may only require initial ventilation until the thoracic cage muscles recover function. During the acute injury phase, patients with high thoracic lesions are highly susceptible to aspiration and pneumonia due to impaired ability to cough or to clear the airway of secretions. Treatment of spinal shock includes high doses of steroids, surgical stabilization of fractures, and supportive care in an intensive care unit setting. Following this stage of flaccid paralysis, SCI patients usually develop exaggerated reflexes with muscle spasms, upper motor neuron-injury pattern tendon reflexes, and autonomic hyperreflexia (AH).

Medical complications in chronic spinal cord-injured women and the impact of pregnancy

Following spinal shock, the situation stabilizes as chronic SCI. Approximately 50% of patients will be an American Spinal Injury Association "A" injury, which is functionally a complete cord transection.[21] The remainder are a mix of sensory sparing/motor nonfunctional/motor functional injuries.[4] Most neurological improvement is made within the first year post

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injury, although some patients make slow progress over the subsequent years.[19,22] Patients with cervical and high thoracic injury levels typically have impaired pulmonary function with decreased respiratory reserve, resulting in poor cough and recurrent pulmonary infections. Renal function may deteriorate due to chronic or recurrent urinary tract infection (UTI) with calculi formation. Deep vein thrombosis (DVT) and decubitus ulcers remain a persistent concern in the wheelchair-bound patient. Anemia of chronic disease is common, and iron supplementation may cause deterioration in bowel function. Many SCI patients have low blood pressure (BP) due to low blood volume as well as impaired capacitance vessel function.[23]

Pregnancy may aggravate many of these conditions (see Table 10.1). Common problems encountered during pregnancy in SCI patients are UTI (45–80%), anemia (10–60%), pressure sores (6–26%), and increased spasticity.[1,4] The respiratory changes of pregnancy, including loss of functional residual capacity and expiratory reserve volume, further compromise cough mechanics, while the expanding uterus limits diaphragmatic excursion. This is important in the patient with cervical cord injury who may be entirely dependent on her diaphragm for respiratory function due to loss of intercostal muscle function. Labor normally puts an enormous demand on ventilation, and may actually cause acute diaphragm fatigue.[24,25,26,27] Although this fatigue does not cause clinical deterioration in the healthy parturient, labor may not be tolerated in the respiratory-compromised SCI patient. Much of the increased minute ventilation in labor is precipitated by the pain of parturition, something which may not occur in parturients with high spinal cord lesions.

As weight increases and ligaments become more lax, transfers may become more difficult. In Jackson's study, 11% of women could not transfer independently at term, and 4.5% were unable to propel their wheelchairs.[4] Pregnancy predisposes to more urinary stasis, resulting in increased UTI rates.[6,28] Intermittent bladder catheterization results in less morbidity than indwelling catheters, but the frequency of catheterization may have to increase with gestation. Orthostatic BP changes may be augmented by the pregnancy-induced decrease in systemic vascular resistance and become symptomatic.

Table 10.1 Medical complications of spinal cord injury aggravated by pregnancy

Pulmonary
Decreased respiratory reserve
Atelectasis and pneumonia
Impaired cough
Hematological
Anemia
Thromboembolic phenomenon
Urogenital
Chronic urinary tract infections
Proteinuria
Renal insufficiency
Urinary tract calculi
Dermatological
Decubitus ulcers
Cardiovascular
Hypotension
Autonomic hyperreflexia

From Crosby, E. T., St. Jean, B., Reid, D. *et al*. Obstetrical anaesthesia and analgesia in chronic spinal cord-injured women. *Can. J. Anaesth*. 1992; **39** 489.

Management of the chronic cord-injured parturient

Antepartum and medical management

Patients with chronic SCI should be assessed prior to conception to determine their ability to tolerate pregnancy. Many SCI patients take medications for spasticity, such as baclofen and diazepam. Baclofen has been used during pregnancy, without untoward effects; however, experience is limited.[29,30] Diazepam was associated with an increased incidence of lip and palate malformations[31] although other studies dispute this.[32] However, a fetal benzodiazepine syndrome has been described, which includes intrauterine growth restriction, dysmorphism, and central nervous system (CNS) dysfunction.[33] In view of this, benzodiazepines should be stopped preconception. Evaluate pulmonary function early in pregnancy to identify women at risk of respiratory deterioration during later stages of pregnancy and labor.[34,35] Pulmonary function tests are recommended and respiratory consultation should be sought if there is significant compromise.[1] Some patients require ventilator assistance during late pregnancy, and negative pressure ventilators are ideally suited to this task. Every effort should be made to assist the SCI patient to cease smoking.

Obstetrical management

Preterm labor is more common in SCI parturients and unattended delivery may occur in women with complete lesions above T10 because of difficulty in ascertaining when labor begins. There is an increased need for assisted delivery because of the loss of abdominal musculature needed for expulsive efforts. [5,6,7,28,36,37,38,39,40] Earlier reports of a high incidence of fetal malformations have not been confirmed.[39] One study found an increased risk of low birth-weight babies beyond the risk of prematurity.[4]

Obstetrical management begins with the assessment of pelvic adequacy, especially in women who suffered the injury before puberty.[1,34] If the pelvis is deemed adequate, vaginal delivery should be anticipated as approximately 50% of SCI parturients will have a spontaneous vaginal delivery, with 30% requiring assistance.[4,41,42] Preterm labor, a known risk in SCI patients, is treated with beta-mimetic tocolytics and magnesium sulfate ($MgSO_4$),[1,38,39] but due to its muscle relaxation effects $MgSO_4$ may precipitate respiratory failure.[43] Women with complete lesions above T10 are at risk for unexpected and unattended delivery, especially if labor begins while asleep. If awake, other symptoms such as increased spasticity or symptoms of AH may alert the woman to the onset of labor.[3] Some centers have routine admission at 36–37 weeks to prevent unattended delivery,[36,44,45] others use frequent tocodynamometry and cervical examinations as term gestation is approached.[15] Home uterine activity

monitoring starting at 26–28 weeks' gestation enables the woman to remain at home.[41] There is consensus that C/S be reserved for obstetric indications. During labor, continue specific nursing care for SCI, such as frequent turning to prevent pressure sores, and optimal bladder care. Education about pregnancy and SCI is important for the patient's physical and mental well-being during labor.

Autonomic hyperreflexia

The most dangerous complication during labor and delivery is AH. Failure to identify patients at risk and provide appropriate prophylaxis and treatment for episodes of AH remains an important medical and legal issue.[1,5,28] In a report of six quadriplegic women who developed AH: one died of an intracerebral hemorrhage, one had significant brain damage, and one suffered an intrauterine fetal death, all due to lack of recognition or poor treatment of AH.[46] The American College of Obstetricians and Gynecologists guidelines published in 2002 recommend early initiation of epidural block to prevent AH in patients at high risk.[1] If epidural block is not available immediately, the guidelines recommend vasodilator treatment. If labor induction is planned, patients at high risk for AH should have an epidural initiated before induction.[1,2,39] Avoid ergonovine in the third stage because hypertension and dysrhythmias may mimic the diagnosis of AH.[36] Of note, the incidence of preeclampsia is not increased in this patient population.[34,47]

Autonomic hyperreflexia, or the mass autonomic response, was first reported in 1890 but not well described until 1947.[5,48] It is a life-threatening reflex caused by a mass sympathetic response to noxious stimuli that is not modulated by the supraspinal influences of the central nuclei.[36,49] Commonly seen in patients with spinal cord injuries at T5 or above (85–90%), it is less common in patients with lesions between T5 and T8 (50–65%), and is rare with lesions below T8.[50] Most patients at risk for AH have complete lesions,[5] as incomplete lesions allow for craniocaudad neural traffic, with the potential for supraspinal modulation of spinal reflexes. This syndrome requires an intact sympathetic system below the level of the lesion, and is not seen in cases of cord infarction.

The reflex is initiated by a noxious stimulus entering the dorsal horn of the spinal cord and passing into sympathetic neurons in the intermediolateral columns of the lateral horns. These sympathetic neurons travel to the paraspinal sympathetic chain, allowing propagation of these impulses in cephalad and caudad directions and peripherally. A large sympathetic outpouring causes vasoconstriction and visceral spasm. The excessive sympathetic response is in part due to the large, disorganized increase in presynaptic terminal boutons that occurs post injury.[51] Spinal levels above the lesion are influenced by supraspinal modulation leading to reflex compensatory vasodilation. However, if the lesion is above the midthoracic level there is insufficient vasodilator reserve to counteract the vasoconstriction, resulting in severe systemic hypertension. Baroreceptor response to the hypertension produces bradycardia and vasodilation above the lesion level.[50,52,53] Clinical signs and symptoms include severe hypertension, headache, bradycardia, sweating, blurred vision, increased skin temperature, facial flushing, and nasal congestion.[2,51] Morbidity from AH includes retinal hemorrhage, intracranial hemorrhage,[43,46,53,54] hypertensive encephalopathy,[53] seizures,[5] atrioventricular conduction abnormalities including sinus arrest,[45,52] fetal dysrhythmias, and uteroplacental insufficiency leading to fetal hypoxemia.[1]

Many patients at risk for AH will give a history of AH episodes with visceral (bladder or rectal) overdistention. Pregnancy may result in increased episodes of AH.[4] Labor is a potent stimulus and AH may be precipitated for the first time during parturition.[5,55,56] There are case reports detailing the manifestation of AH as waxing/waning headaches with each contraction, with the headaches being used as an indicator of the efficacy of labor epidural analgesia.[57] Maximal noxious stimulation occurs in the perineal region innervated by S2–4, and AH may not present until perineal stretching occurs in the late first stage or early second stage of labor.[36,52] Other stimuli include vaginal examinations, instrumentation, amniotomy, and oxytocin infusions.[2] The differential diagnosis of hypertension in SCI parturients is preeclampsia. The two differ clinically with AH having a sudden onset and episodic hypertension, coinciding with contractions. The lack of proteinuria, characteristic of preeclampsia, also helps to confirm the diagnosis.[58]

Anesthetic management of labor and delivery

Problems in SCI patients of relevance to the anesthesiologist include an increased incidence of premature labor and painless, precipitous labors, the need for labor analgesia, the occurrence of muscle spasms in labor, the frequent requirement for assisted delivery, prophylaxis for AH, potential for hypotension, and hyperkalemia with succinylcholine in those with subacute injury. Anesthesia during the spinal shock phase of SCI can be very challenging. Unopposed vagal parasympathetic activity puts the woman at high risk for severe bradycardia during airway manipulation, including suctioning. Usually general anesthesia (GA) is required for surgery during this period of instability. [51]

Antepartum anesthesia consultation is encouraged and should be routine for parturients with SCI.[2,36] During this visit, the need for analgesia and the risks and benefits of the different methods should be discussed. Concerns about worsening symptoms following regional anesthesia should be addressed, and the benefits of regional anesthesia for those at risk of AH emphasized. Patients with complete injury levels above T5 have painless labors and are at high risk for developing AH, whereas those with complete lesions between T5 and T10 are at reduced risk. Although, patients with an injury level below T10 generally experience normal labor pain, those with incomplete lesions between T6 and T10 may not have typical labor pain, but may be subject to extreme leg and abdominal spasms with contractions.

There are several options for treating AH during labor. Initial reports recommended the combined use of anxiolytics with antihypertensives.[28] Control of BP was not optimal, but there was no reported morbidity attributable to the AH. Labor analgesia was not considered necessary in most SCI patients. Direct arterial vasodilators such as sodium nitroprusside and hydralazine have

been used with varying success, as have calcium channel, ganglionic (trimethaphan), and adrenergic (guanethidine, prazosin) blocking agents.[59,60] First-line agents include sublingual nifedipine 10 mg, transdermal nitroglycerin, and phentolamine.[51] Clonidine may be useful when significant spasticity is a problem.[51] There is one report on the use of $MgSO_4$ to treat AH.[61] Because the hypertension may be episodic in labor-induced AH, maternal BP may be very high during contractions despite antihypertensive medication, then very low in the intervening period before the onset of the next contraction. Beta-blocking agents are not recommended because of possible uterine vessel vasoconstriction, although the combined alpha/beta-blocker labetalol has been used successfully.[36,45] The literature overwhelmingly supports epidural analgesia as the method of choice for prophylaxis and treatment of AH in labor.[1,2,6,34,36,44,51,62,63,64,65,66,67,68,69]

The timing of epidural analgesia is controversial. Although some propose initiation of the epidural block only when signs of AH are detected, most recommend a prophylactic epidural block initiated at onset or during induction of labor.[1,2,34,44,59,66] It is prudent to use dilute local anesthetic solutions to minimize hypotensive effects. An initial concentration and infusion rate of bupivacaine for prevention of AH and provision of labor analgesia is 0.080–0.125% at 8–10 ml/h. The rate can be altered to control pain or AH symptoms. Patient-controlled epidural analgesia is an option for the parturient who needs analgesia. The role of lipid-soluble narcotics is uncertain, but if fentanyl is employed it should be used as an adjunct to local anesthetic as epidural fentanyl alone was ineffective in one case report.[70] Meperidine has local anesthetic properties and can be given as a bolus of 1 mg/kg epidurally or 0.25 mg/kg intrathecally to treat AH.[2,71] Adults with SCI are not at increased risk of latex allergy and therefore do not require special protocols.[72]

Regional anesthesia in the cord-injured parturient

Neither stable neurological disease nor a history of major spinal surgery represent absolute contraindications to regional anesthesia. There may be technical difficulties in performing the block in parturients with abnormal anatomy, as well as an increased risk of accidental dural puncture or inadequate and failed blocks.[73] Careful assessment of the upper end of the block is mandatory, as are frequent BP measurements. If the block is below the lesion level it cannot be defined unless segmental abdominal reflexes are intact. In those cases, lightly stroking the sides of the abdomen above and below the umbilicus will initiate muscular contraction causing the umbilicus to move towards the stimulus. Regional blockade will stop this reflex activity. In patients with spastic paraparesis, the level of the block becomes apparent with loss of spastic activity.[63] Invasive monitors are not required routinely but may be indicated in specific situations. Pulse oximetry is recommended in patients with high cord lesions who are receiving neuraxial opioids. Securing the epidural catheter adequately is essential due to increased sweating, secondary to AH. A liquid adhesive and steri-strips along the epidural catheter in addition to the usual dressing is usually effective. As AH may occur up to 48 hours postpartum, the epidural catheter should be left *in situ* postpartum.[51]

Regional anesthesia may cause significant hypotension in women with borderline BP due to the combined effects of SCI and pregnancy.[71] Although SCI patients are near-maximally vasodilated as a baseline state, the use of dilute local anesthetic solutions for labor analgesia negates the need for a mandatory preepidural fluid bolus. One should carefully titrate the analgesia level upward while montoring vital signs. Treatment of hypotension is with intravenous (i.v.) fluids and then, if needed, careful administration of vasopressors. Both i.v. ephedrine (2.5–5 mg bolus) and i.v. phenylephrine (20–50 μg bolus) are safe. If the woman has signs of AH and has been given antihypertensive agents, one needs to be careful of interactions with the subsequent use of vasopressors. Ephedrine may have reduced efficacy in the presence of beta-blockade, and an exaggerated effect if ganglionic-blockers have been administered. High thoracic levels of epidural or spinal block, due to unpredictable changes in the epidural and spinal compartments, may not be well tolerated in quadriplegics as they typically have no expiratory reserve volume.[51] Techniques that allow titration of local anesthetic are best: epidural catheters, spinal catheters, combined spinal–epidural (CSE).

Nursing assistance is required to position and support the patient for epidural and spinal insertion. Patient mobility and presence of contractures or spasms will determine the best position. Once an epidural block is established the woman should be repositioned every 30 to 60 minutes to prevent pressure sores.

There is no consensus on appropriate monitoring techniques for the laboring SCI patient. Because of the low baseline BP and possibility of AH, routine use of invasive hemodynamic monitors (arterial line, central venous pressure) has been advocated.[34] The author does not share this view and is of the opinion that noninvasive monitoring techniques are adequate in the majority of cases.

Anesthesia for cesarean section

The choice of anesthetic technique for C/S is influenced not only by maternal condition and surgical procedure, but whether anesthesia is required for AH prophylaxis. These patients should be seen in consultation early in pregnancy to discuss anesthetic options, risk of AH, and to assess respiratory function. Regional block is required primarily to provide AH prophylaxis through visceral anesthesia in patients with high cord injury (above T5). Encourage gentle surgical manipulation of the viscera to minimize the risk of an AH crisis. Avoid uterine exteriorization, if possible. Postoperatively regional anesthesia is beneficial for AH prophylaxis as well as providing analgesia. Spinal anesthesia may be technically easier to perform than epidural anesthesia but it is harder to control anesthesia levels, hypotension may be more problematic, and respiratory mechanics may be impaired. Some authors recommend against its use for these reasons.[51,69] However, spinal block does provide consistently better sacral anesthesia than epidural block.[74,75]

General anesthesia prevents AH when deep enough to prevent response to noxious genitourinary stimuli. Tracheal intubation will not initiate AH. Rapidly acting i.v. antihypertensive agents such as sodium nitroprusside and labetalol should be available.

Succinylcholine is associated with massive hyperkalemia when administered 72 hours post injury and up until six months or more after the injury. Hyperkalemia likely results from the proliferation of extrajunctional neuromuscular receptors on the denervated muscle.[40] Nondepolarizing muscle relaxants are recommended for tracheal intubation and maintenance during GA for all SCI patients in the first year post injury.

Patients with high cord lesions may require intensive management and should be cared for in centers capable of offering such treatment. Staff must be educated about the issues relating to care of the SCI patients, in particular AH.

Spinal cord tumors and vascular malformations

Spinal cord tumors are very rare in women of childbearing age, representing less than 12% of nervous system tumors diagnosed during pregnancy. Less than 50 cases have been reported in the literature and excluding vertebral hemagiomas, the majority are benign lipomas, with an assortment of primary and metastatic tumors comprising the remainder.[76,77] Presenting symptoms of spinal column and cord compression (back pain, fatigue, sciatica) may be attributed to the normal changes of pregnancy.[77] Severe and/or persistent back pain or neurological symptoms should be investigated. Symptoms often worsen immediately postpartum, and may be attributed to regional anesthesia.[78] Diagnostic imaging should not be delayed because of pregnancy, and radiographic shielding should be maximized when possible. Magnetic resonance imaging (MRI) is the preferred imaging method.[76] Once the diagnosis is made, decompressive laminectomy and tumor excision for nonvascular tumors should be performed expeditiously to limit long-term neurologic deficits.[77]

Vascular malformations such as vertebral hemangiomas and arteriovenous malformations (AVM) of the spinal cord are more common than predicted from the number of symptomatic cases. Spinal cord tumors are often confused with vascular malformations, as pregnancy increases vascularity of mengiomas and hemangiomas. The physiologic impact of labor and delivery, and the vascular and blood volume changes of pregnancy may alter the course of the vascular malformation. There is little specific information about anesthetic management of these cases, and common sense must apply to decisions regarding anesthetic options for labor and delivery.

Primary and metastatic malignant tumors

Meningiomas are the most common reported cases of spinal cord tumor occuring during pregnancy, usually comprising 25% of all spinal cord tumors.[79,80] Meningiomas, especially of the spinal variety, are more common in women than men and some are hormonally responsive.[81] Spinal meningiomas are typically slow growing; however, as they are frequently vascular pregnancy may cause a sudden increase in size. There is no evidence that the incidence of spinal meningiomas is increased by pregnancy, a preexisting one is simply more likely to become symptomatic.[80] Presenting symptoms of a spinal meningioma are: sensory changes (80%), gait instability (68%), and back pain or radicular pain.[79] The tumors are usually located anterolaterally, laterally, or posterolaterally to the cord and most are completely intradural and in the thoracic region.[79,82] Surgery usually leads to a good functional outcome, although younger patients with spinal meningiomas tend to have more aggressive histological subtypes than patients older than 50 years.[79]

There are six reported cases of spinal meningioma diagnosed during pregnancy.[80] In five of the six reported cases, surgery was performed postpartum, and all had good to excellent neurological recovery. All six patients had lower limb weakness and/or gait instability at presentation.[80]

Astrocytoma, sarcoma, and ependymoblastoma have also been reported.[78,81] Metastatic tumors include melanoma, osteosarcoma,[83]and invasive moles (see Figure 10.1).[84,85]

There are no guidelines regarding optimal delivery time for women with spinal cord tumors; however, the need for radiotherapy or chemotherapy for malignant tumors influences the decision. Some tumors may progress rapidly, and even with surgery the parturient may be left with significant spinal cord injury. The same principles discussed earlier in managing SCI parturients should be applied.

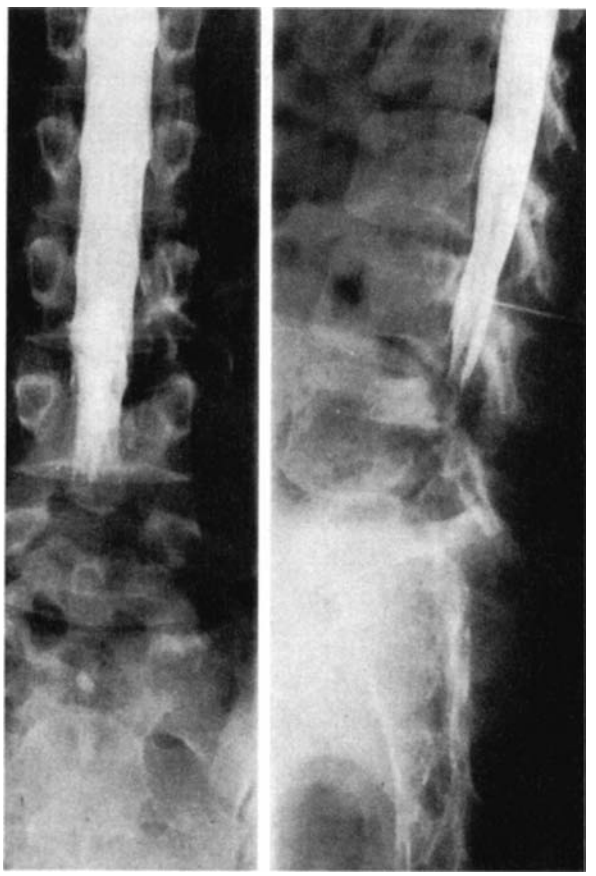

Figure 10.1 Metastatic invasive mole. Lumbar myelogram showing an extradural obstruction extending distally from the lower margin of the L4 vertebral body. Reproduced with permission from Makangee, A., Nadvi, S. S. & Van Dellen, J. R. Invasive mole presenting as a spinal extradural tumor: case report. *Neurosurgery* 1996; **38**:191–3.

Benign tumors including neurofibromas

Benign spinal cord tumors include cellular schwannomas, neurolemmomas, lipomas, and neurofibromas associated with von Recklinghausen disease.[86,87,88,89,90] Typically these tumors are slow growing, and there is no evidence that they become more symptomatic during pregnancy. There has been one case report each of cellular schwannoma and neurolemmoma diagnosed during pregnancy. The women presented with back or hip pain with subsequent radiation into a leg.[86,87] Both underwent surgical laminectomy postpartum with good neurological recovery. Another woman presented two days postpartum with severe back pain. She had a thoracic neurinoma that had bled, producing acute spinal cord compression.[91] Her neurological recovery was not complete despite early surgical intervention. Neurofibromas, associated with von Recklinghausen disease, are discussed in Chapter 8.

Spinal lipomas, intradural, not associated with spinal dysraphism, are very rare comprising less than 1% of all spinal tumors. There have been less than ten pregnancy-associated cases reported worldwide.[89,90] These are slow-growing benign tumors that usually have a long history of vague sensorimotor disturbances prior to diagnosis and intervention, with spastic paraparesis developing later. Three cases that presented peripartum had symptoms ranging from two to twelve years previously, and all deteriorated during pregnancy or shortly after delivery.[89] Two of these women had midthoracic lesions, the other a cervicothoracic lipoma: all were located typically in the posterior aspect of the spinal cord. Diagnosis was made with computerized tomography (CT) scan, followed by MRI. All patients underwent decompressive laminectomy postpartum: complete resection of lipomas is not possible due to the close adherence to the spinal cord.

There are a few cases of spinal hemangiolipomas presenting during pregnancy. One patient was not diagnosed until nine years postpartum when symptoms recurred, another patient was finally investigated following her tenth pregnancy despite symptoms appearing during her ninth pregnancy.[92] Both cases presented with paraparesis during pregnancy and recovered completely postpartum. The relapsing clinical picture is typical for this kind of tumor.

Vascular tumors and other arteriovenous malformations

Angiomas and hemangiomas comprise the largest group of reported spinal cord tumors in pregnancy, and are overrepresented compared to the general population.[81] The theory is that the pregnancy-induced combination of increased blood volume and venous pressure in the vertebral vascular plexus makes angiomas clinically symptomatic.[93,94] Symptoms are either secondary to compression or thrombosis/hemorrhage within the angioma.[76,77] These vascular spinal tumors are likely to present in the third trimester.[81,95,96] Symptoms may improve postpartum and recur in a subsequent pregnancy if surgery was deemed unnecessary.[81] There is one case report of the successful use of spinal anesthesia for C/S in a patient with a known C3 spinal cord AVM/angioma.[97] Epidural anesthesia was avoided because of concerns about precipitating cord ischemia by a rise in epidural space pressure. The associated commentary by two obstetrical anesthesiologists, however, suggested that spinal anesthesia (and epidural anesthesia) was not a safe option for spinal cord angioma/AVM.

There are approximately 17 reported cases of vertebral (bony) hemangiomas producing cord compressive symptoms during pregnancy, the majority of them located in the upper thoracic regions of the spinal cord.[95,98] Presentation is usually during the third trimester, when the gravid uterus compresses the vena cava, engorging the extradural venous plexus with a decrease in spinal column perfusion pressure.[99] One woman presented with leg weakness and sensory loss immediately postpartum. The labor epidural was initially blamed, but clinical deterioration led to an MRI, which revealed a T11 compression fracture secondary to a hemangioma (see Figure 10.2).[95] Autopsy specimens of the general population reveal that 10% have undiagnosed angiomas of the vertebral column.[77] Symptoms often diminish or disappear postpartum, so unless there is acute cord compression, some feel it is reasonable to wait for fetal viability, perform a C/S, and then reassess the need for surgical intervention.[98] Hemangioblastomas of the spinal cord associated with von Hippel-Lindau disease are located intramedullary, are of varying size, and may bleed during pregnancy.[100] Mode of delivery and use of regional anesthesia are controversial in neurofibromatosis (see Chapter 8).

Similar to vascular spinal cord tumors, cardiovascular changes during pregnancy, labor, and delivery may cause dural AVM to become symptomatic. Dural AVM comprise approximately 5% of all spinal space-occupying lesions.[101] Similar to angiomas, dural AVM often produce symptoms with exercise and certain postures.[102] However, the symptoms are more likely to be gradual in onset, as opposed to catastrophic, suggesting a bleed.[101] Venous hypertension probably causes edema and secondary ischemia of the spinal cord. The average age at presentation is 57 years compared to 37 years for spinal cord angiomas, therefore this vasular tumor is less likely to occur during pregnancy.[102] There is one case report of a cervical dural AVM (undiagnosed) becoming symptomatic with initiation of labor epidural analgesia. The theory is that epidural injection caused a change in blood flow through the cervical AVM causing cord ischemia.[103] There are two reports of similar cord ischemia symptoms from an undiagnosed thoracic dural AVM following the use of lumbar epidural anesthesia,[104,105] and one case following the use of spinal anesthesia in an older male with a subsequently diagnosed dural AVM.[106] The consequences of an AVM bleed can be catastrophic, requiring expeditious neurosurgical decompression. However, dural AVM are less likely to bleed than spinal cord angiomas.[102]

Differentiation between vascular tumors of the spinal cord and AVM of the dura or vertebral body has not been clear in the past due to poor quality imaging techniques and surgical/histological descriptions. Localization as intradural, extradural, or vertebral may prove more useful in terms of risks of complications of compression and ischemia versus hemorrhage.

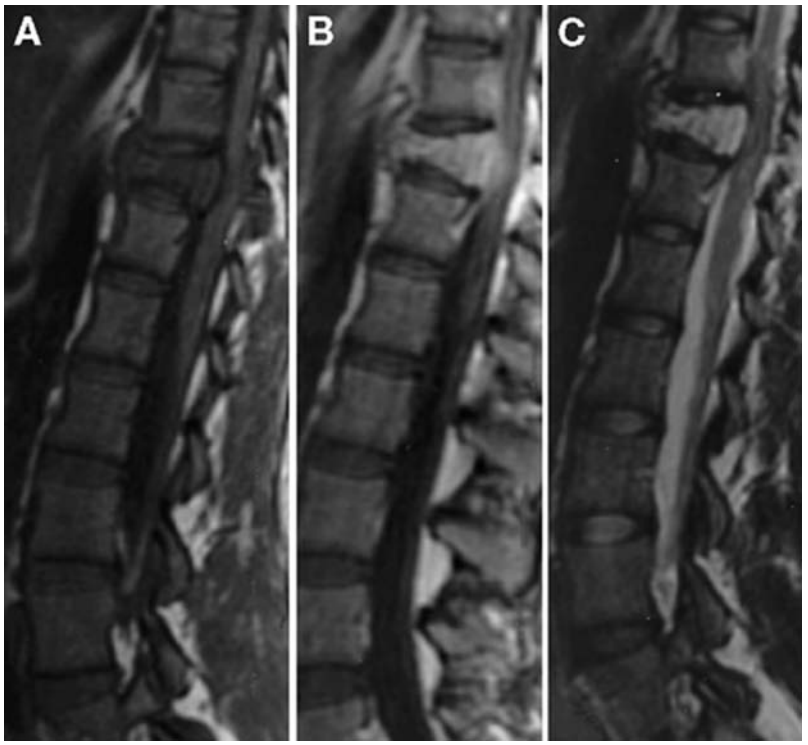

Figure 10.2 Sagittal MRI of T11 vertebral fracture with spinal cord compression due to vertebral hemangioma during pregnancy. Image A is T1-weighted image. Image B is gadolinium enhanced. Image C is T2-weighted. Reproduced with permission from Schwartz, T., Hibshoosh, H. & Riedel, C. Estrogen and progesterone receptor-negative T11 vertebral hemangioma presenting as a postpartum compression fracture: case report and management. *Neurosurgery* 2000; **46**: 218–21.

Anesthetic management of the parturient with spinal cord tumors and AVM

Regional anesthesia/analgesia

Parturients who have had recent surgery on their vertebral column/neuroaxis may be unwilling to have neuraxial anesthesia. Residual tumor, scarring, and inflammatory changes may make regional techniques less reliable.[83] There have been serious neurological sequelae following the use of regional anesthesia in patients with occult or known spinal tumors,[103,107,108] so most authors consider a spinal cord tumor to be a contraindication to the use of regional anesthesia.[77,83,86,87] Those with known vascular malformations of the spinal cord should not have epidural or spinal anesthesia. Not only is there a risk of an epidural hematoma from direct trauma, but changes in cerebrospinal fluid (CSF) pressure from a dural puncture or epidural bolus injection may change the vascular wall stresses preciptitating hemorrhage or edema with subsequent cord compression or cord ischemia. In addition, "normal" hypotension from spinal anesthesia may cause spinal cord ischemia from critical changes in perfusion pressure or possibly a steal phenomenon.[102,103]

Anesthesia for cesarean delivery

Elective C/S is usually chosen for parturients with spinal cord tumors or vascular malformations, because of the concern about effects of labor on intra-abdominal and intrathoracic pressures with subsequent changes in blood flow in the tumor/AVM.[97] The paucity of cases in the literature, with the large variation in diagnosis and presentation, make it impossible to draw a conclusion about the best mode of delivery. A case conference involving consultants from neurosurgery, obstetrics, and anesthesia is recommended for these parturients. General anesthesia is the recommended anesthetic technique.[77]

Degenerative spinal cord diseases

Spinal muscular atrophy

Pathophysiology and effect on pregnancy

Spinal muscular atrophy (SMA) is a group of inherited, usually autosomal recessive, neuromuscular disorders in which the anterior horn cells of the spinal cord degenerate. The estimated incidence is 1:10 000 making it the second most common autosomal recessive disorder in Caucasians after cystic fibrosis. Type I (Werdnig-Hoffman disease) is the most severe form presenting at birth with death usually within 2 years. Type II presents in childhood with rare survival to adulthood. Type III (Kugelberg-Welander disease) is the "mild, chronic" form of the disease. Most pregnant women with SMA have Type III disease; however, there are case reports of pregnancy in Type II SMA, which typically means more severe disease in the parturient.[109,110,111,112] The classic features of SMA are weakness and atrophy of the proximal muscles of the lower limbs, more than the upper limbs, with fasciculations. Gait instability is common, as are fine, irregular tremors of the upper limbs. Most patients are wheelchair dependent by their third decade in Type III disease, earlier in Type II. There are often significant respiratory effects due to involvement of the intercostal and accessory muscles of respiration. Secondary kyphoscoliosis may be severe, adding to the restrictive pulmonary defect; many women will have undergone spinal instrumentation for scoliosis correction.[113,114] Cranial nerve involvement is seen in less than 20% of patients with SMA. There is a case report of a parturient with SMA

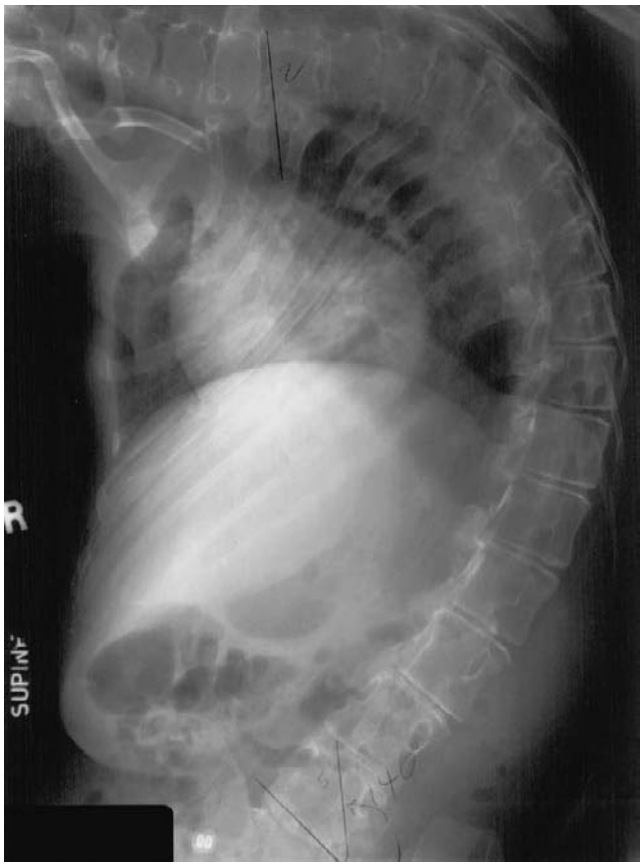

Figure 10.3 Antero-posterior plain x-ray postpartum showing severity of kyphoscoliosis and distorted intrathoracic contents in a woman with SMA Type II. Reproduced with permission from Yim, R., Kirschener, K., Murphy, E. *et al*. Successful pregnancy in a patient with spinal muscular atrophy and severe kyphoscoliosis. *Am. J. Phys. Med. Rehabil*. 2003; **82**: 222–5.

Type II and vocal cord paralysis.[115] This woman had a forced vital capacity (FVC) of 2.1 L, 54% of predicted value. She had a low forceps delivery with epidural analgesia, as she was unable to perform Valsalva maneuvers due to the vocal cord paralysis.

Muscle weakness may worsen during pregnancy usually after the second trimester, and respiratory failure may occur necessitating ventilation. In a series of twelve patients with SMA, eight had worsening of muscle weakness after the second trimester, and five reported permanent loss of muscular strength postpartum.[116] Unfortunately, anesthetic techniques were not discussed. Respiratory function tests should be repeated in the third trimester to capture changes in respiratory function that may not be apparent in the wheelchair-bound patient. Yim described a successful pregnancy and delivery in a woman with SMA who had a FVC of 400 ml, severe kyphoscoliosis (140° curvature), and body weight of 31 kg.[117] She did not require invasive ventilatory support as the pregnancy progressed; however, she did require increasing noninvasive ventilatory support. An elective C/S was performed at 34 weeks' gestation as she could not eat adequately, secondary to shortness of breath. Of note, she had a tracheostomy, which likely decreased her work of breathing compared to other published case reports of similarly affected parturients with SMA who required invasive ventilatory support as pregnancy progressed (see Figure 10.3).

Cesarean section is the mode of delivery in most cases, as parturients with SMA may have a contracted pelvis and lack the expulsive power to push.[110,111,112,113,114,117,118,119] Postpartum recovery is often prolonged in women with SMA, and overall there is a high rate of complicated pregnancies and deliveries (83% in Rudnik-Schoneborn's series).[116]

Anesthetic considerations for labor and delivery

Both regional and general anesthesia have been used in SMA. There are no contraindications to regional analgesia in this chronic neurodegenerative disease; however, there are some challenges. Previous spinal instrumentation can create technically challenging blocks, as well as a higher chance of inadeqate or failed blocks.[73,112,114,120] Continuous spinal anesthesia is an option, providing a titratable block that is more likely to be complete than epidural anesthesia. Epidurals, single-shot spinals, and CSE have all been used or tried in these patients without subsequent deterioration in neuromuscular status.[104,115,119,121] Positioning of the parturient for a regional technique can prove challenging due to residual scoliosis and hip flexion contractures.

The degree of respiratory compromise must be considered carefully prior to providing a high thoracic block, as removal of already marginally functioning intercostal muscles may lead to inability to cough or maintain an adequate tidal volume.[122,123,124]

Possible complications of GA in the parturient with SMA include: prolonged neuromuscular blockade with subsequent need for ventilation, potential for acute hyperkalemia following succinylcholine,[125] and the effects of residual anesthesia plus lower abdominal surgery on return of FVC in a patient with preexisting respiratory compromise. Avoidance of neuromuscular blocking agents would be ideal.[111]

Amyotrophic lateral sclerosis

Pathophysiology and effect of pregnancy

Amyotrophic lateral sclerosis (ALS), also known as Lou-Gehrig disease, is a progressive neurodegenerative disease affecting the anterior horn cells of the spinal cord. It primarily affects men, and is typically diagnosed after the fifth decade of life with a prevalence of 2:100 000; however, there have been approximately 12 cases reported since 1993 of pregnancy in women with ALS (see Table 10.2).[126,127,128,129,130,131,132] The incidence of ALS has been increasing, beyond that predicted for the aging population. Multiple variants of ALS are now recognized, revealing considerable heterogeneity in the disease presentation and course.[133] Approximately 5–10% of cases are inherited as an autosomal dominant gene. The median survival after diagnosis is 19 months, and female sex is associated with worse disease.[134] Typical symptoms start with loss of fine motor function in the upper limbs, fasiculations, and cramping. The disease progresses to involve the legs, followed by the muscles of the tongue, pharynx, and larynx. Higher cortical function remains intact. Parasympathetic activity for bowel and bladder function remains relatively intact, as does ocular activity (see Table 10.3).

Table 10.2 ALS and pregnancy

Authors	Age	Pregnancy	ALS onset	ALS course during pregnancy	Mode of delivery	Infant status	ALS course postpartum
Levine, 1977	36	2nd	6th month GA: dysarthria, dysphagia, upper limb weakness	Slow progression	SVD	Healthy	Slow deterioration
	38	3rd	2 years before	Slow progression	SVD	Healthy	Slow deterioration
MoretJurilli, 1991	27	1st	Prepregnancy. At time: severe tetraplegia, dysarthria, dysphagia	Slight worsening	C/S 39 weeks under spinal	Healthy	Not stated
Lupo, 1993	28	3rd	36 weeks GA: R hip and foot weakness	Rapid worsening	C/S	Healthy	Died 6 weeks postpartum respiratory failure
	33	5th	1 year prepregnancy: tetraplegia, respiratory failure	No clinical worsening	PROM 33 weeks. SVD	Healthy	Stable 1.5 years later
Vincent, 1995	27	2nd	2 months prepregnancy	Worsening. Appearance of bulbar signs	C/S	Healthy	Stable
Jacka, 1997	31	1st	8 weeks GA: lower limb weakness	Worsening. Tetraparesis and respiratory failure at 32 weeks	C/S epidural	Healthy	Tracheostomy and PEG 1 week postpartum
Tyagi, 2001	29	1st	6th month GA: difficulty walking, dysarthria	Slight progression	SVD	Healthy	Not stated
Chio, 2003	27	1st	6th month GA: weakness and atrophy hands, gait	Slight progression	SVD epidural	Healthy	Progressive
	29	1st	5th month GA: atrophy R quadriceps	Slight progression	SVD	Healthy	Slight progression
	33	2nd	3rd month GA: shoulder girdle weakness	Rapid progression with respiratory impairment	Abortion	n/a	Died 3 months after abortion
	38	3rd	6th month: R hand atrophy	Mild progression	C/S 34 weeks general	Healthy	Slowly progressive
Sobrino-Bonilla, 2004	32	2nd	1 year prior to pregnancy	Rapid progression	Vacuum assisted vaginal. Epidural	Healthy	Not stated
Leveck, 2005	25	3rd	14 weeks GA: L sided weakness, severe dysphagia	Rapid progression with respiratory failure 29 weeks, no motor function 34 weeks	Vacuum assisted vaginal		Died 9 months postpartum

GA = gestational age; SVD = spontaneous vaginal delivery; C/S = cesarean section; R = right; L = left; n/a = not applicable; PROM = Premature rupture of the membranes; PEG = Percutaneous endoscopic gastrostomy

Modified from: Chio, A., Calvo, A., Di Vito, N. *et al.* Amyotrophic lateral sclerosis associated with pregnancy: report of four new cases and review of the literature. *ALS and Other Motor Neuron Disorders* 2003; **4**: 45–8.

Table 10.3 Clinical features of adult-onset motor neuron disorders

	Amyotrophic lateral sclerosis	Progressive muscular atrophy	Spinal muscular atrophy	Primary lateral sclerosis	Kennedy disease	Progressive bulbar palsy	Monomelic amyotrophy	Brachial amyotrophic diplegia
Typical distribution of weakness	Asymmetrical Distal	Asymmetrical Distal	Symmetrical Proximal or distal	Asymmetrical Distal	Symmetrical Proximal	Initially limited to bulbar muscles	Asymmetrical Restricted to 1–2 extremities	Symmetric proximal upper extremities
UMN signs	Present	Absent	Absent	Present	Absent	Present	Absent	Absent
LMN signs	Present	Present	Present	Absent	Present	Present	Present	Present
Sensory loss	Absent	Absent	Absent	Absent	Modest	Absent	20%	Absent
Genetics	AD (10%) SOD mutation (2%)	Unknown	AR, AD, SMN gene implicated	Unknown (no reported familial cases)	XLR CAG repeats >40	Unknown (no reported familial cases)	Unknown	Unknown
Distinct features	UMN and LMN signs with usually rapid progression	Pure LMN disorder with usually indolent course	Pure LMN disorder usually with progressive proximal weakness over decades	Pure UMN disorder with indolent course	Gynecomastia, diabetes mellitus, impotence, infertility	Weakness initially limited to bulbar muscles. May progress rapidly to ALS or be relatively indolent	Progression over 2–3 years with subsequent stabilization Typically young age of onset	Preservation of respiratory and bulbar function with slow progression

Abbreviations: Autosomal dominant (AD); Autosomal recessive (AR); Cytosine – adenine – guanine nucleotide (CAG); Lower motor neuron (LMN); Superoxide dismutase (SOD); Survival motor neuron (SMN); Upper motor neuron (UMN); X-linked recessive (XLR)

Reproduced with permission from: Strong, M. & Rosenfeld, J. Amyotrophic lateral sclerosis: a review of current concepts. *ALS and Other Motor Neuron Disorders* 2003; **4**: 136–43.

The largest series describing ALS in pregnancy is from a 1956 study in Guam, where the incidence of ALS is 100 times the expected rate.[135] In this series, 17 women underwent 21 pregnancies, all had vaginal deliveries. Some women with very advanced ALS at the time of conception died during their pregnancy. There appears to be no specific effect of pregnancy on the course of ALS, nor any special obstetric complications.[135] This is supported by case reports, where pregnancy did not alter median survival.[126,127,128,130,136] However, as disease progression is rapid, it should be expected that the parturient will decline during pregnancy. One case report describes a 25-year-old woman presenting at 22 weeks' gestation with left-sided weakness of 8 weeks' duration, as well as severe progressive dysphagia.[131] She had a marked decrease in respiratory function (FVC 53%). By 29 weeks' gestation she required a tracheostomy because of inability to clear secretions. By 34 weeks' gestation, despite plasmapheresis, she had no motor function. Labor was induced and she had a healthy baby, but the woman died nine months postpartum.[131]

The respiratory demands of pregnancy may result in acute respiratory failure in women with ALS. Establishment of baseline respiratory function early in pregnancy, with regular follow-up by a respirologist is necessary. Pulse oximetry during labor is recommended, as the additional respiratory stress from labor may be poorly tolerated.[130] Again, there is no specific treatment for ALS; however, plasmapheresis has been tried. Supportive therapy during pregnancy includes provision of adequate nutritional support.[137] Vaginal delivery should be expected, as the pelvic floor is relaxed and uterine contractility unaffected.

Anesthetic considerations for labor and delivery

There is essentially no information in the literature about the anesthetic management of the parturient with ALS. Most case reports deal with the obstetrical management and do not include anesthetic data. However, in 1998 Jacka described epidural anesthesia for C/S in a primiparous woman with familial ALS who developed respiratory failure at 32 weeks' gestation.[128] This patient required bilevel positive airway pressure (BiPap) postoperatively, but tolerated a T4–5 intraoperative block reasonably well with a $PaCO_2$ of 70 (55 preoperatively). This woman developed acute respiratory failure ten days postpartum requiring long-term ventilation.

Epidural anesthesia has been used successfully in nonparturients with ALS.[138,139,140] One must weigh the risks of using regional anesthesia in a patient with active progressive neurological disease versus the benefits, recognizing that new neurological deficits postpartum are likely due to the disease. Epidural morphine has been used for postoperative analgesia, notably in a woman undergoing hysterectomy for endometrial carcinoma.[139] This patient had significant preoperative respiratory compromise with an FVC of 34% of that predicted, but had no difficulty tolerating a T5 block, or the epidural morphine.

General anesthetic considerations must include airway protection because of bulbar dysfunction, avoidance of succinylcholine, sensitivity to nondepolarizing muscle relaxants (so avoid if possible), and depression of respiratory function post anesthesia or surgery.

Postpolio syndrome

Pathophysiology and effect on pregnancy

Postpolio syndrome (PPS) is a degenerative disease of the anterior horn cells of the spinal cord. It is estimated that there are between 250 000 to 300 000 polio survivors in the USA. Postpolio syndrome usually develops 25–30 years after the original infectious episode.[141] Until recently, the diagnosis of PPS required a history of paralytic polio; however, PPS can occur in those patients exposed to polio who only suffered a mild, flu-like illness. The diagnosis of PPS is one of exclusion, after ruling out other adult-onset motor neuron disorders (see Table 10.3).[142,143]

Typical symptoms include leg-length discrepancy, asymmetric progressive weakness, limping, and scoliosis. However, the most prominent symptom is fatigue: both generalized and secondary to peripheral muscle weakness.[142,144] Muscle pain occurs in up to 80% of affected individuals, and nerve compression syndromes in 49%.[145] Women are more likely than men to suffer from muscle and joint pain. Cold intolerance is another feature of PPS.[144] Electromyelography (EMG) shows typical widespread neurogenic changes in all four limbs. Despite the mildness of the original polio, PPS can be full-blown and have a significant effect on daily living. The cause of PPS is not clear, but is likely due to degeneration of enlarged motor neurons, which have grown in response to the original polio, within an overall population of reduced motor neuron units.[146] Postpolio syndrome tends to be a slowly progressive disease: respiratory effects and dysphagia are the most concerning features.[147]

Similar to the other degenerative motor neuron diseases, the respiratory muscles are often significantly affected in PPS, and bulbar symptoms result in laryngeal dysfunction with inability to protect the airway.[141]

There are only three reported cases of pregnant women with PPS, all of whom had severe respiratory disease requiring noninvasive ventilation prepregnancy.[148] All had successful term pregnancies, with vaginal deliveries not requiring anesthesia. Vital capacities (VC) ranged from 240 to 280 ml and were not affected by the pregnancy. Clearly earlier recommendations about avoiding pregnancy when VC is less than one litre did not hold true.[149]

Anesthetic considerations

There is limited information about the anesthetic management of patients with PPS, although a good review has been published.[144] There are only two case reports in the English language literature that discuss anesthesia in patients with PPS. One case was uneventful, but in the other a 51-year-old woman died after suffering a postoperative cardiac arrest.[141,150] The cause was thought to be secondary to a respiratory arrest from sensitivity to opioids combined with undiagnosed sleep apnea, both part of her PPS. Awareness of the potential for significant respiratory compromise, bulbar dysfunction, sensitivity to anesthetic agents, and cold intolerance are important; otherwise, general principles of anesthetic management are based upon the patient's physiologic and neurologic status.[141,144] There is no scientific data to support theoretical concerns of neurotoxicity of local anesthetics

in patients with PPS, therefore the choice of regional versus general anesthesia is an individual decision.

Transverse myelitis

Transverse myelitis is a rare inflammatory disease of the spinal cord, associated with infections and autoimmune disorders such as systemic lupus erythematosus (SLE). There are eight published cases of pregnancy in patients with transverse myelitis, one secondary to schistosomiasis infection.[28,39,151,152,153,154,155] The most common presenting symptom is back pain with progressive paraparesis. Management includes specific therapies for the underlying disease, high doses of steroids, and plasmapheresis.[155]

If patients with transverse myelitis have complete physiologic spinal cord transection, they should be treated as SCI patients. Obstetrical complications include preterm labor, unattended delivery, and UTIs. Autonomic hyperreflexia is a potential risk.

Friedreich ataxia

Friedreich ataxia is an uncommon inherited neurodegenerative disease affecting the spinocerebellar tracts. It is fully discussed in Chapter 8.

Spinal dysraphism

Spinal dysraphism describes a variety of congenital abnormalities, which arise as a result of failed closure of the neural tube. It is divided into: spina bifida cystica (or aperta), which includes meningocele, myelomenigocele, rachschisis, and anencephaly; and spina bifida occulta, which encompasses a wide range of minor defects of mesodermal, neural, or ectodermal origin (see Figure 10.4, Table 10.4). The solitary finding of defective laminar arches, which may itself be a variant of normal, is not usually described as spina bifida occulta.[156] The incidence of spina bifida cystica varies from 0.5 to 2.5 per 1000 births in North America and the UK respectively, but is decreasing due to folate supplementation preconception and improved antenatal screening.[157] The incidence of spina bifida occulta ranges from 10 to 50% of the adult population based on the presence of radiological defects in the vertebral spinous processes and lamina.[158,159]

Early repair of meningoceles and myelomeningoceles, as well as advances in the treatment of the complications such as infection and hydrocephalus, has resulted in an increasing number of spina bifida cystica patients reaching childbearing age.[158] There are numerous case reports describing the management of labor and delivery in these patients.

Spina bifida occulta

A CT scan of patients with low back pain or sciatica found spina bifida occulta at S1 in 207 of 1200 patients aged 18 to 72 with a decreased incidence in the older patients. Of the patients with occulta lesions, 82% had posterior disc herniation at L4–5 or L5–S1.[159] Another study found a high incidence of lumbar disc degeneration in young patients with spina bifida occulta. These patients were all less than 20 years old, and 54% had lumbar disc disease at L3–4, L4–5 or L5–S1.[160] Sixty percent of spina bifida occulta occur between L4 and S2 levels.[161] The clinical significance of isolated bony arch abnormalities is not yet established, but spina bifida occulta has been associated with chronic back problems, enuresis, and neurological problems reflecting its many variants.[159]

Magnetic resonance imaging improves the diagnosis of occult spinal dysraphism, defining lesions missed on plain radiographs.[162,163] The anomalies detected include tethered cord, diastematomyelia, syringocele, and diplomyelia. Patients with cord abnormalities have cutaneous stigmata in 50–70% of cases, but only 30% are symptomatic.[163,164,165] Patients with isolated vertebral arch anomalies usually have neither cutaneous stigmata nor underlying cord anomalies.[161]

Table 10.4 Forms of spina bifida occulta according to tissue of origin

Mesodermal	Neural	Ectodermal
Defective laminar arch	Distal hydromyelia	Nevi
Diastematomyelia	Spinal cord adhesions (without obvious cause)	Hairy patches
Intra/extradural bands	Meningocele manque (aborted herniation of nerve roots)	Dermal sinuses
Lipomas		Cutaneous dimples
Dermoid cyst		

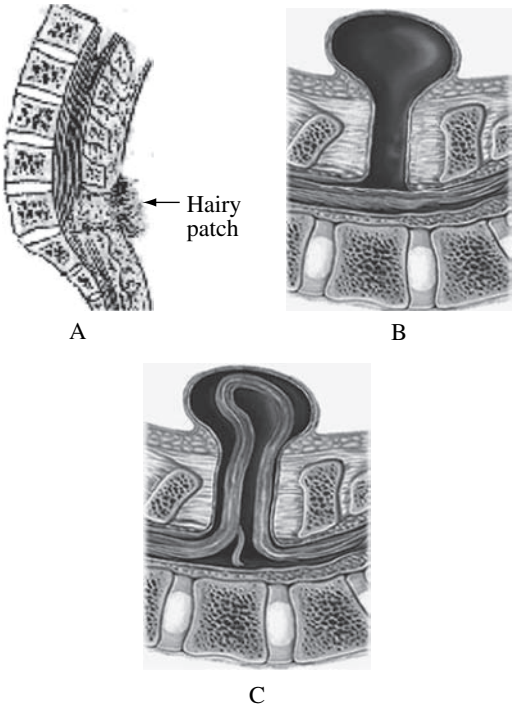

Figure 10.4 Grades of spina bifida. A: spina bifida occulta; B: meningocele; C: myelomeningocele.

Anesthetic management of patients with spina bifida occulta

There are few implications for obstetrical anesthesia management of the patient with spina bifida occulta. Most cases are asymptomatic and consist of an isolated bony defect at a low spinal level. Regional anesthesia is not contraindicated, and the only recommendation is to perform the block at a site remote from the level of the anomaly. There is an increased potential for accidental dural puncture as the supporting ligaments, specifically the interspinous ligament and the ligamentum flavum, may be abnormal at the lesion.[166] The epidural space may be discontinuous at this point and inadequate or failed blocks may result.[157]

Patients with occulta lesions who have underlying cord anomalies often have cutaneous signs, and may have neurological signs and/or symptoms. These patients should be assessed antepartum by an anesthesiologist so that relevant neurological data and consultations can be obtained. This also provides an opportunity to discuss issues relating to regional anesthesia, such as direct trauma to the low-lying tethered cord, an increased potential for problem blocks, and dural puncture. The majority of spina bifida occulta lesions are at low lumbar or sacral levels, and are fairly trivial anatomic anomalies that have little impact on regional anesthesia. If symptoms (leg pain and weakness with or without cutaneous stigmata) suggest a tethered spinal cord (see tethered cord syndrome), an MRI should be obtained prior to performing neuraxial anesthesia, to determine the level of termination of the spinal cord.[167]

Spina bifida cystica

The long-term outlook for patients with spinal bifida cystica has improved[168,169] since a large-scale study from 1983 noted a 48% early mortality rate.[170] Most spina bifida cystica patients have surgery in the first 24 hours of life. Improved surgical techniques and better treatment of infection and hydrocephalus have reduced early mortality to 3–8%. However, approximately 24% of infants born with spina bifida cystica will die by early adulthood, with the later deaths mainly attributable to shunt malfunction.[171] Most patients develop hydrocephalus (a Chiari II malformation is usually associated with significant cystic lesions) but not all require placement of shunts. There is a lower incidence of tethered cord syndrome due to improved closure techniques, although by age ten, 19% of patients experience some cord tethering.[171] A follow-up study of spina bifida cystica patients operated on between 1978 and 1986 found that 84% of patients were ambulatory,[168] reflecting the fact that repaired lumbar meningoceles usually have only mild neurological deficits confined to the lower limbs.[166]

There are associated anomalies of the gastrointestinal, skeletal, cardiac, and renal systems that may affect development.[172,173] Myelomeningocele is a dynamic neurological disease that eventually produces orthopedic, neurologic, and genitourinary complications. Progressive spinal deformities occur in up to 90% of patients, with findings of scoliosis, kyphosis, and lordosis.[171,174] Developmental paralytic scoliosis is the most common resulting from an imbalance of the paravertebral muscles. This form of scoliosis usually undergoes rapid progression with growth.[175,176] Congenital scoliosis also occurs due to bony abnormalities such as hemivertebrae and multiple rib fusions. Progression is slower, and often significant kyphosis is present. Tethered cord syndrome may also cause scoliosis.[177] The surgical treatment consists of releasing the tethered cord and spinal instrumentation. The release of a symptomatic tethered conus often arrests progression of the curvature in patients with lumbosacral but not thoracic lesions.[174] Progressive lordosis and kyphosis are also significantly reduced.

Deterioration in function may occur in spina bifida cystica because of development of syringomyelia or shunt dysfunction.[177] Many patients have poor hand control and manipulative difficulties despite the distance of the lesion from the cervical cord.[178]

Impact of pregnancy on spina bifida cystica

There are several features of spina bifida cystica that affect the course of pregnancy and delivery (see Table 10.5). The management of patients with significant kyphoscoliosis is discussed in Chapter 7. Spina bifida cystica patients are often less mobile during pregnancy as their weight increases, making them more susceptible to DVT and decubitus ulcers. The changes in the lumbosacral spine resulting from hormonal relaxation of the ligaments and the expanding abdominal girth may adversely affect wheelchair fitting and mobility.[179] Impaired renal function may worsen due to the increased incidence of UTIs. An increase in abdominal pressure created by the expanding uterus may impair diaphragmatic function in the spina bifida cystica patient, especially those of short stature or with scoliosis. Diaphragm fatigue during labor may occur, resulting in the need for ventilatory support and operative delivery.[149]

Table 10.5 Neurological and structural residua in adults with spina bifida

Abnormality	Implications for pregnancy and delivery
Sacral agenesis	May permit vaginal delivery despite small pelvis.
Pelvic abnormalities (contracted, misshapen)	Abnormal lies and presentations that may preclude vaginal delivery.
Short stature	Respiratory problems as uterus expands. More likely to have C/S.
Scoliosis (may be severe)	Cardiorespiratory. Mobility problems. Technical difficulties with regional anesthesia.
Tethered cord syndrome	Neurological deterioration. Cord trauma with regional anesthesia.
Shunts	Raised ICP. Infection.
Chronic bladder problems	Worsened during pregnancy. Renal impairment.
Motor and sensory deficits	No labor pain. Autonomic hyperreflexia. Precipitous labor.

C/S = cesarean section; ICP = intracranial pressure

Medical and obstetrical management

Patients with spina bifida cystica should consult with medical and obstetric personnel prior to conception to ensure the medical aspects of their disease are optimized. There is no clear evidence that there is an increased risk of fetal abnormalities in women with spina bifida cystica, but there are case reports from past decades documenting fetal malformations.[180,181] Genetic counseling preconception is recommended. Respiratory function should be assessed, and followed in patients with compromise and those at risk for decompensation during the pregnancy. Patients with shunt-controlled hydrocephalus require assessment of shunt function and the sites of peritoneal drainage should be noted. A survey of shunt-dependent women found that 9 of 70 women had an increase in headaches during pregnancy.[182] Seven women required shunt revisions during pregnancy, and 23 patients experienced shunt failures in the first six months postpartum.

Many spina bifida patients have short stature and/or a contracted pelvis that may preclude vaginal delivery, so the pelvis should be assessed early in pregnancy. Patients may have had prior pelvic x-rays, usually for orthopedic evaluations and these may be suitable to assess pelvic adequacy.[183]

Latex sensitization and allergy affect up to 72% of children with spina bifida cystica if exposed to latex since birth.[184] Recognition of this serious problem resulted in latex avoidance measures with a large decrease in the prevalence of latex sensitization;[185,186] however, the current adult population with spina bifida have a high likelihood of latex allergy.

There are numerous case reports dealing with management of pregnancy and parturition in spina bifida cystica. Some common complications include preterm labor, UTIs, difficult pelvic examinations due to leg contractures, and problems in those patients with uretero-ileostomies (damage during C/S).[180,183,187,188,189] There is consensus that C/S should be performed for obstetric reasons only.[183]

Anterior sacral meningocele is an extremely rare form of spina bifida cystica that may not be diagnosed until puberty or even during pregnancy (compression of neural sac by growing uterus). Implications for pregnancy include associated sacral and coccygeal malformations, and the effect of the sacral mass on delivery.[166,188]

Anesthetic management

Regional anesthesia is not contraindicated in patients with fixed neurological deficits, or previous spinal surgery. Although it may be more technically difficult, a high success rate for labor epidural analgesia in patients with spinal instrumentation can be achieved with prudent persistence.[73,190] There is concern about potential increased rates of accidental dural puncture and incomplete blocks.[179,189] Some recommend performing the epidural above the lesion level, if possible, to decrease the likelihood of an abnormal epidural space and hence dural puncture.[189] Use of the hanging drop or air balloon technique to identify the epidural space may be more effective if abnormal ligaments are present, although relatively few anesthesiologists have experience with these techniques.[189] The local anesthetic dose requirements in spina bifida patients may be decreased. Theories to explain this finding include altered dural permeability and abnormally small volume epidural space surrounding the lesion.[165,188] Tidmarsh published sixteen cases of spina bifida, both occulta and cystica, of whom ten received a labor epidural.[157] Six blocks were uncomplicated and provided good analgesia; however, four were less than ideal: one dural puncture, one high block, and two provided inadequate caudal analgesia. Additional sacral analgesia may be necessary, such as a pudendal block.

Some consider spinal anesthesia contraindicated because of the unpredictability of local anesthetic dose requirements.[166,179] On the other hand, Brome[191] and Nuyten[190] successfully used spinal anesthesia for C/S. Both authors opined that spinal anesthesia is technically easier and provides a more predictable block. Nuyten used a spinal catheter to manipulate the level of block.[190] The risk of cord damage by needle insertion is minimal if one chooses a site below the anatomic lesion level.

If the patient has a shunt, confirm appropriate shunt function and normal intracranial pressure (ICP) before performing neuraxial block.[182] In spina bifida cystica patients with a lesion level above T5–7, there is the potential for AH during labor. However, such lesions are extremely rare as they usually occur with other CNS malformations that are incompatible with life.

An increasing number of spina bifida cystica patients will have children in the future, and the management issues specific to this syndrome must be recognized. These patients require antepartum assessment by an anesthesiologist so that all options are analyzed and discussed. Obstetric anesthetic care of the spina bifida patient provides many challenges. In its mildest form, spina bifida occulta, there may be an increased risk of accidental dural puncture while performing epidural blocks. The more severe spina bifida cystica patients may present with significant scoliosis, surgically scarred backs, respiratory compromise, as well as obstetric problems such as preterm labor and pelvic abnormalities that preclude vaginal delivery. In the past, most patients did not receive regional anesthesia for labor and C/S was often performed under GA. An increasing number of reports document successful epidural and spinal anesthesia in these patients.[157,179,188,189,191] There is an excellent review of the anesthetic considerations for the parturient with a neural tube defect.[192]

Syringomyelia

Syringomyelia is a neurological disorder characterized by the formation of cystic cavities within the spinal cord, typically in the cervicothoracic regions. Syringomyelia most often is congenital, associated with Chiari I malformations (see Figure 10.5).[193] The pathogenesis is unclear. However, 84% of patients have craniocervical junction abnormalities, which may be the initiating cause of the cystic lesions because of the development of a craniospinal pressure gradient. Other causes of syringomyelia include trauma, arachnoiditis, and spinal cord tumors.[194,195,196,197] Traumatic syrinxes following obstetric epidural and spinal anesthesia have been described with all of the patients suffering neurological symptoms from the cystic lesion.[198,199]

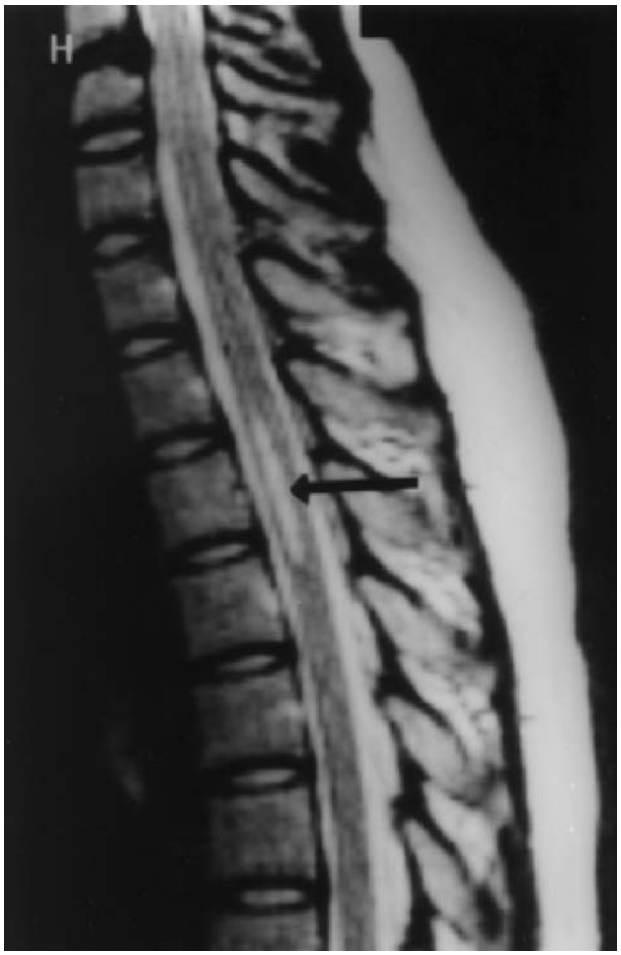

Figure 10.5 T2-weighted sagittal MRI of the upper spinal cord showing a syrinx typical of syringomyelia. Reproduced with permission from: Murayama K. Cesarean section in a patient with syringomyelia. *Can. J. Anesth*. 2001; **48**: 474–7.

Syringomyelia is classified as communicating (with CSF pathways) or noncommunicating. Communicating syringomyelia is considered more susceptible to deterioration when exposed to raised ICP.[200] Extension of the syrinx cephalad into the medulla is known as syringobulbia.

Typical symptoms of syringomyelia are progressive sensorimotor deficits of the upper limbs, and often neuropathic pain. Pain and temperature are commonly affected, while touch and position sense are usually preserved. Diagnosis is made based upon clinical features, supported by MRI, and often is not made until patients are in their third or fourth decade. Secondary kyphoscoliosis due to weakness of the paraspinal muscles is common; however, the development of this structural abnormality may be reduced by early suboccipital craniectomy.[193] Arai *et al.* showed that syringomyelia and Chiari malformation may be diagnosed during investigation of progressive scoliosis in children.[201] There have been cases of terminal syringomyelia associated with occult spinal dysraphism. Obviously these cases will have lower limb, rather than upper limb, neurological deficits.[164,195]

Syringomyelia is a progressive myelopathy in two-thirds of affected patients. The physiologic changes of pregnancy and labor pose a theoretical risk of brain-stem herniation and cord compression,[202,203] although neither of these complications has been reported. There is a paucity of literature on the obstetric and anesthetic management of women with syringomyelia. The largest series by Mueller involved seven women, from which it appears that pregnancy does not affect the symptoms of the disease and vice versa.[203] A review of Chiari I malformations, with or without syringomyelia, in 12 parturients revealed no untoward effects from vaginal delivery.[204] The decision about mode of delivery should be made in consultation with a neurosurgeon, and will depend upon maternal symptoms during pregnancy.[202,203]

Anesthetic considerations for labor and delivery

The most important pathophysiologic features are neurologic dysfunction and respiratory impairment secondary to kyphoscoliosis. Even in parturients without hydrocephalus, one must be concerned about the effects of sudden increases in ICP on the cystic cavities typical in syringomyelia. Sudden clinical deterioration in patients with syringomyelia following a short period of Valsalva maneuver has been documented in the past.[205] Involvement of the autonomic system in patients with syringomyelia is common, especially if syringobulbia is present, resulting in altered cardiovascular responses to vasodilation and hypovolemia. Slow induction of regional anesthesia/analgesia is recommended.[200,202,205]

The flow dynamics of CSF are very abnormal in syringomyelia, therefore spinal anesthesia is unpredictable, and continuous spinal anesthesia would be a better choice. Some authors consider a Chiari malformation and/or syringomyelia an absolute contraindication to regional anesthesia, some only to spinal anesthesia.[194,196,206,207,208,209] There is one case report of a Chiari I malformation diagnosed two weeks postpartum in a woman who developed nystagmus following a large-gauge-needle dural puncture.[210]

Fear of large-gauge dural puncture with an epidural needle and the subsequent alterations in CSF pressure leading to brain herniation are theoretical, but possible. However, epidural anesthesia has been used successfully for labor analgesia and C/S in several cases of syringomyelia with or without a Chiari malformation.[202,203,205] Nel *et al.* reported on the uneventful use of epidural anesthesia for C/S in a woman diagnosed with a Chiari I malformation three months prior to becoming pregnant.[205] She refused decompression surgery, had worsening headaches during pregnancy and so had an elective C/S.

The presence of a shunt for hydrocephalus, or syringomyelia alone, is not a contraindication to regional anesthesia. However, 13–23% of parturients may experience shunt problems during pregnancy, some requiring revision, others waiting until postpartum.[182,211] Neurosurgical consultation is recommended. Prophylactic antibiotics are often recommended, as is a shortened second stage. One should enquire about clinical features of raised ICP prior to using neuraxial anesthesia.

Considerations for GA include avoidance of succinylcholine, sensitivity to nondepolarizing neuromuscular agents,[207] involvement of bulbar nerves affecting airway reflexes, effects of respiratory compromise on postoperative course, and control of ICP.

Interestingly, some authors feel that GA should be avoided in these patients secondary to concerns about sudden increases in ICP during induction and emergence.[202] Roelofse *et al.* reported on C/S under GA (they considered regional absolutely contraindicated) in a parturient with syringomyelia, who awoke with new sensory disturbances that resolved within 24 hours.[208] There were no specific measures to control ICP during the anesthetic.

Tethered cord syndrome

Tethered cord syndrome (TCS), also known as "tight filum terminale," "cord traction syndrome," "filum terminale syndrome," and "tethered conus," was first described in 1953 by Garceau, although it was probably reported as early as 1918.[212,213] It is a neurological syndrome caused by longitudinal traction on the conus medullaris. Initially recognized in pediatric postmeningomyelocele repair patients, it is an accepted, albeit rare, entity in adults. There are over 200 case reports of patients presenting between the ages of 17 and 76 with a mean age of symptom onset of 30–33 years and a mean age of diagnosis of 37–39 years.[214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233] Tethered cord syndrome is commonly associated with spinal dysraphism, with varying degrees of incomplete fusion of the neural arch. Other anomalies include spina bifida occulta (the most frequent finding in adults),[215,221] diastematomyelia, syringomyelia, lipomas, dermoid cysts, intra- and extradural bands, and meningocele manque.[216,217,231,234]

The underlying pathology causing cord tethering includes thickened filum terminale (33–69% of cases),[235] intradural lipoma, spinal adhesions, and postsurgical fibrous bands. A thickened filum terminale is the most common finding in adults, although there is often more than one pathological finding. Almost all children who have had a meningocele repair have evidence of a thickened filum and/or low placed conus medullaris, yet only 15% develop TCS.[212,236,237] The onset of symptoms is related to the degree of traction on the conus. Symptoms in adults occur in two patterns: there is direct trauma to the spine or momentary excessive stretching of the tight conus by extreme flexion of the neck or hips; or a pattern of longstanding mild and static neurological symptoms that suddenly progress or worsen.[167,222,231] In the largest published series on adult-onset TCS, 44% followed the second pattern.[222] Some postmeningocele repair patients do not present with TCS until adolescence, and do not fit either of the above patterns.[212,226,237]

Recognizing that many patients with TCS reach adult age prior to becoming symptomatic from spinal cord dysraphism, Yamada recommended a new classification of TCS.[167] Group 1 (10/70 patients in Yamada's 2000 series) are those with known spinal dysraphism since birth but stable neurologically until adulthood. Group 2 (60/70 patients) are those who were asymptomatic during childhood, developing neurological symptoms after their teenage years, with no evidence of other spinal dysraphic features. The majority of these Group 2 patients are in fact "failed back syndrome" patients, in whom a tethered cord was not recognized as the cause of chronic back pain with neurological symptoms. Both groups manifest similar symptoms; however, neurological improvement following surgery is much more impressive in Group 2 patients.[167]

In adults, the major complaint is pain[230] (80% in study by Pang and Wilberger[222]), usually in the lower limbs and perineal region. In most adults the lower back and leg pain is worsened upon performing the "three B signs" described by Yamada *et al.*: (1) sitting in the "*B*uddha" postion, (2) difficulty *B*ending slightly at the waist while performing tasks such as dishwashing, and (3) holding light material like a *B*aby at waist level while standing.[167] Other presenting symptoms include sphincter dysfunction (57%), leg weakness and sensory deficits (65%), as well as trophic ulcerations.[219,220,221,222,227] Cutaneous stigmata of spinal dysraphism such as dorsal midline nevi, lipomas, skin tags, dimples, and hairy patches are found in only 50% of adult TCS but are very common in childhood TCS.[216,217,238] Similarly, foot deformities and progressive scoliosis are unusual in adults and more common in children. Often a precipitating event, such as childbirth (lithotomy position), sexual intercourse, motor vehicle accidents causing hip flexion, exercising and weight lifting,[220,232] lumbar spondylosis and herniated discs, direct blows to the back, and falls on the buttocks,[222] initiates the symptoms of adult-onset TCS.

The most useful diagnostic tools are CT scan and MRI, with MRI now the imaging method of choice (see Figure 10.6).[219,220,221,224,230] Myelography will demonstrate the position of the conus medullaris as well as the classical horizontal or cephalad direction of exiting sacral nerve roots. It does not delineate well the underlying cause. Plain radiographs of the spine reveal vertebral anomalies in more than 95% of adults.[217,222,223] Use of CT scans, MRI or direct examination at surgery reveals that 70% of adult patients have elements of spinal dysraphism, other than spina bifida occulta.[217] Initial descriptions of the syndrome required that the conus be in an

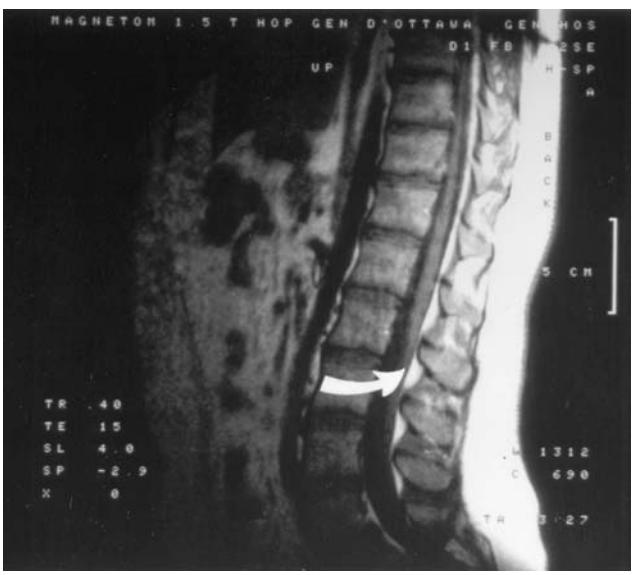

Figure 10.6 MRI scan of 23-year-old female with a tethered spinal cord. White arrow indicates conus medullaris, located at the level of the L3 vertebral body.

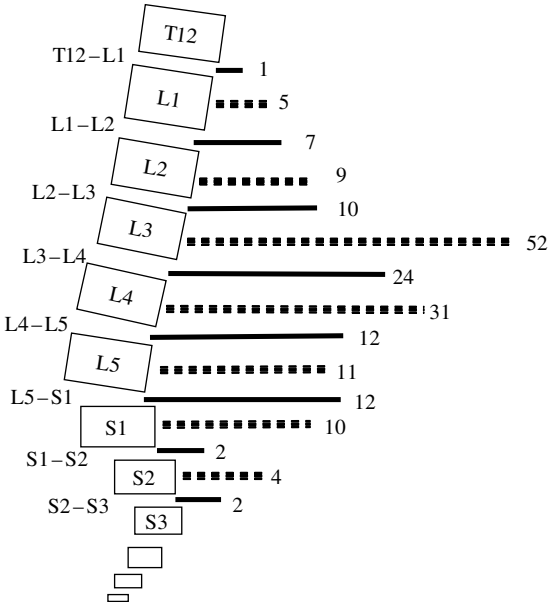

Figure 10.7 Graph shows distribution of the positions of the coni in 229 patients with tethered cord syndrome. Data from references 232,247,254.

abnormally low position, defined as below the body of L2.[213,222] However, in adults 15–35% of patients with TCS will have a normally positioned conus (see Figure 10.7).[167,217,223] One study classified patients with TCS as Group 1 and 2 and found that the conus is below L2–3 in all Group 1 patients, but only 65% of Group 2.[167] Magnetic resonance imaging shows that in almost all adults with TCS, the conus is posteriorly displaced within the spinal canal and attached to the posterior arachnoid membrane.[239] This conus position means extreme care must be taken during epidural or spinal anesthesia, as direct needle trauma is more likely than if the conus was merely low lying.

Surgical release of the filum terminale relieves tension and results in dramatic improvement in pain symptoms and motor and sensory function. Unfortunately, sphincter function often remains impaired.[216,222] Despite this, neurosurgeons now recommend surgical intervention in adults diagnosed with TCS. [167,214,232,233,235]

Although rare, adult-onset TCS does occur during the childbearing years.[219,221,222,225,232] In Huttman *et al.*'s series of 54 cases of TCS, 11 presented as adults, and of those 5 experienced first symptoms during pregnancy and/or delivery.[232] The presenting symptoms of back pain and urological problems may delay diagnosis of the syndrome or result in misdiagnosis.[219,233] The underlying pathology frequently discloses the presence of spina bifida occulta, and in 85% of cases the conus medullaris ends below the body of L2. Evidence for adult-onset TCS includes the presence of static neurological deficits from childhood; pain in the perineal, anal, and gluteal regions, or the lower limbs, which may worsen with prolonged bed rest; shock-like sensations up and down the spine on forward bending similar to Lhermitte's sign; bilateral lumbosacral sensorimotor deficits; cutaneous stigmata; and bladder complaints with spastic symptoms predominating over hypotonic symptoms.

There are two case reports of young, female patients presenting with classic lumbar disc symptoms of radicular pain and dermatomal sensory loss.[224] One had spina bifida occulta at L3–4, the other had normal plain x-rays. Both had a low-lying conus at L4 and neither had cutaneous stigmata. Another case report involved a woman with a history of persistent back pain and bladder symptoms following a previous pregnancy.[225] She had no cutaneous stigmata, spina bifida occulta at S2, and low-lying conus. The underlying pathology of her TCS was a choriostoma. Another case report described a woman with a history of giant lumbar hairy nevus who developed new unilateral neurological symptoms following delivery with epidural analgesia.[240] On MRI she had a tethered cord and, on clinical examination after delivery, a smaller right foot and absent ankle jerk. The precipitating factor of the new neurological symptoms could have been fetal head compression, position during childbirth, or the epidural itself. Another parturient with known congential lumbosacral lipomyelocele had an MRI during pregnancy that revealed a tethered cord at L4, the same level as the intraspinal lipoma. An epidural was placed at L2–3 for labor analgesia, knowing that caudal spread might be impaired. The epidural was successfully topped up for surgical anesthesia 18 hours later. There were no new neurological symptoms postpartum.[241]

Anesthetic management in parturients with tethered cord syndrome

Clinically, the importance of this syndrome lies in the greater potential for direct spinal cord trauma while performing regional anesthesia, due to the low-lying and posteriorly displaced conus medullaris. This is especially important given the recent evidence that anesthesiologists tend to be at least one level higher than they think when performing regional anesthesia.[242] Also, the syndrome may not become symptomatic until there is a precipitating event such as childbirth, following which regional anesthesia may be implicated. The risks of epidural anesthesia in this group of patients are unknown.

As TCS may not be diagnosed until adulthood it is important to take a careful history and perform a neurological examination in all parturients requesting regional anesthesia who complain of significant back pain or neurological symptoms. In patients with known TCS, regional anesthesia is not contraindicated but should be performed below the level of the conus if known, or as low as possible if not. Informed consent in these patients should include a discussion on the increased risk of spinal cord trauma. Direct needle trauma to the conus does not necessarily produce typical lancinating pain,[199,236] but such pain on performing a regional technique mandates immediate removal of the needle or catheter. Epidural anesthesia may be safer than spinal anesthesia because of the low fixed spinal cord. Intrapartum management of patients with known TCS should include avoidance of prolonged lithotomy position and squatting.

Anterior spinal artery syndrome

Anterior spinal artery syndrome (ASAS) is a rare neurological syndrome caused by occlusion of the anterior spinal artery,

usually in the lower thoracolumbar cord area.[243,244] First reported in 1909, ASAS describes a constellation of neurological symptoms (dissociated sensory function with preservation of proprioception and light touch, and loss of motor function) caused by occlusion of the anterior spinal artery. Often the onset of neurological symptoms is preceeded by sharp back pain.[245] Pathophysiological events leading to ASAS include vessel occlusion, marked vasoconstriction, or local interference with spinal cord blood flow. It is usually seen in the older atherosclerotic population associated with aortic reconstructive surgery, or associated with significant hypotension in the presence of major regional anesthesia. It may occur in younger patients with underlying vasculitic diseases (see Table 10.6).

Spinal cord blood supply is derived from the anterior and posterior spinal arteries. A single anterior spinal artery supplies the anterior two-thirds of the spinal cord, areas which subserve motor and coarse sensory function (see Figure 10.8). It originates at the foramen magnum from branches of the vertebral arteries and, during its course down the spinal cord, receives contributions from seven to ten radicular arteries. It does not have a well developed continuous course, and the feeder arteries from the descending aorta are variable.[107] The major supply in the lower thoracic and lumbar cord is from the artery of Adamciewicz, which enters the cord between T5 and L4. If the artery enters high there are few thoracic medullary vessels, and less vascular supply to the thoracic cord. The paucity of supply and poor anastomoses between the anterior and posterior spinal arteries create watershed areas in the cord where supply to the spinal cord is tenuous, most notably the lower thoracic spinal cord.

Anterior spinal artery syndrome is diagnosed on the basis of a combination of clinical findings and radiographic evaluation. Clinically, there is usually sudden onset of progressive paraparesis, bladder dysfunction, and sensory loss to pain and temperature. Some patients experience pain in the neck or back prior to onset of neurological symptoms.[246] Magnetic resonance imaging has replaced myelography and angiography of the spinal cord as the diagnostic technique of choice.[243] Treatment to reverse the process is limited to high-dose steroids for vasculitis,[247] or anticoagulants and antiplatelet agents for embolic phenomena.[248] In one report, three patients in the acute phase were given injections of dexamethasone and urokinase directly into the artery of Adamciewicz with good results.[246] Recovery from the syndrome is limited in those patients with occlusive lesions, aortic disorders, and angiomas. Residual bladder dysfunction often remains, even when there is improvement in motor and sensory function.[246]

There are case reports of anterior spinal artery thrombosis in younger patients with a vascular malformation of the cord.[249] There is one report of a diabetic patient with scleroderma who

Table 10.6 Reported causes of anterior spinal artery syndrome[a]

Most frequent (greater than 20 cases)
Thoracic aneurysm repair
Abdominal aneurysm repair
Less frequent (10 to 15 cases)
Epidural epinephrine use
Syphilis
Spinal cord angioma
Rare (less than 10 cases)
Thrombosis
Postinfectious
Metastatic cancer
Cervical spondylosis
Mitral valve emboli
Hypotension
Postsympathectomy
Vigorous exercise
Spontaneous epidural bleed
Intravenous vasoconstrictor use

[a] Excluding 17 cases of unknown etiology.
Data from references: 96,106,243,244,245,246,247,248,249,250,251 252,253,256,258.

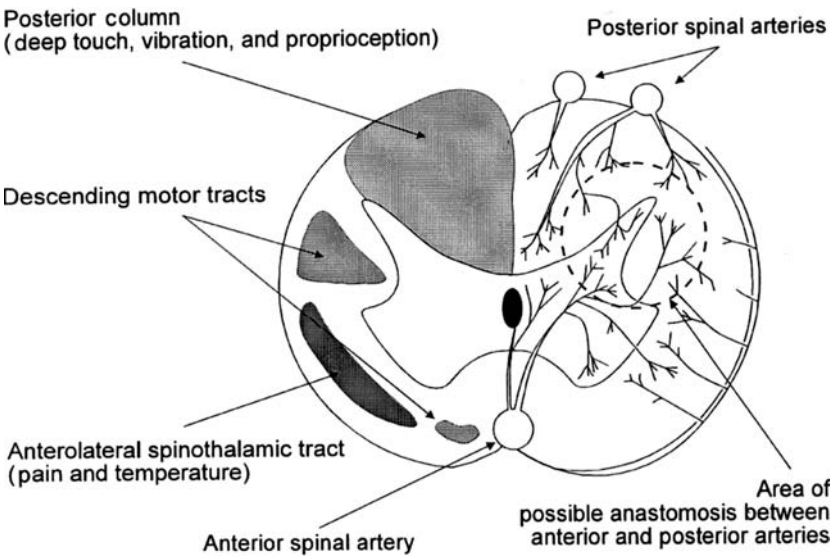

Figure 10.8 Cross-section of the spinal cord showing arterial blood supply and areas of sensorimotor function.

developed ASAS following epidural anesthesia for C/S.[250] There was no hypotension during anesthesia, and the patient was noted to be paraparetic 12 hours after the effect of the epidural abated. An epidural hematoma was ruled out, but the epidural venogram revealed a compressed, collagen-filled epidural space with poor venous supply. It was postulated that local anesthetic injection produced a sudden marked rise in epidural pressure, which caused compression of the vascular supply. There are three case reports implicating epidural catheter irritation as a cause of vasospasm of the anterior spinal artery or segmental feeder arteries. Two involved an epidural for labor analgesia.[245,251] In one case, a woman for elective C/S had an L3–4 epidural placed.[245] During advancement of the catheter she complained of paresthesias in her arms and legs. The catheter was used, but with each top-up the patient complained of similar pain. General anesthesia was administered, but on emergence the patient had persistent paralysis, diagnosed ultimately as ASAS.[245] The second patient developed sudden onset of paraparesis with preservation of posterior column function shortly after delivery.[251] The epidural catheter was removed and there was complete resolution of the neurological symptoms over 30 minutes. In the final case, postoperative analgesia provided by an epidural caused a similar transient ASAS.[252]

There are three cases of spontaneous ASAS presenting in the peripartum period. A primigravida at 32 weeks' gestation presented with rapid and profound paralysis.[96] She had preservation of posterior column function, and negative myelograms and CT scans. After two months she had nearly complete neurological recovery. Another woman presented 20 days postpartum with similar sudden onset of cervicothoracic pain followed by paraplegia.[253] She remained paraplegic. Neither patient had risk factors other than the hypercoagulability of pregnancy, and neither had received a regional anesthetic. Unfortunately, arteriograms were not done, therefore any intrinsic abnormalities of spinal cord arterial supply are unknown. The third case is a woman who, seven days after an uncomplicated labor epidural, developed classic ASAS.[245] Investigations included a CT scan, myelogram and EMG, which led to the diagnosis of ASAS. She had normal coagulation status at the time of delivery.

The addition of vasoconstrictors, such as epinephrine, to local anesthetic solutions for major regional anesthesia is postulated to cause vasoconstriction of the anterior spinal artery resulting in ASAS.[254,255] There are 11 cases of paraplegia following epidural anesthesia attributed to the use of epinephrine.[256] However, dog studies have demonstrated that clinically relevant concentrations of epinephrine in the epidural space do not cause sufficient impairment of spinal cord blood flow to result in ASAS.[107,257]

In the presence of preexisting disease of the spinal arteries, or periods of significant hypotension, epinephrine in the epidural space may cause sufficient vasoconstriction of the anterior spinal artery to impair blood flow and cause ASAS.[107,256] There is one case report of ASAS in a parturient who received a labor epidural infusion containing bupivacaine with 1:400 000 epinephrine.[258] Less than two hours after the infusion had been initiated, a C/S was required for fetal reasons. In the operating room, the woman was hypotensive for a short period (BP decreased from 110 to 86 mmHg) with a bilateral T10 block. After stabilization with a fluid bolus, she was given 5 ml of 3% chloroprocaine for the C/S. She developed classic ASAS diagnosed six hours postoperatively, the MRI at 48 hours showing an ischemic spinal cord from T4 to L1.[258] There were no underlying abnormalities of the spinal cord. The authors postulated the combination of brief hypotension and an epinephrine-containing epidural infusion was the cause of the ASAS. Many parturients experience the same conditions without developing ASAS, however.

In the childbearing population, arteriosclerosis is uncommon but diseases with vasculitic components such as SLE, scleroderma, and Takayasu arteritis may be present and can affect spinal cord blood flow.[247] In these patients it is prudent to avoid the use of epinephrine or other vasoconstrictors in the epidural or subarachnoid spaces. Vigilance in the detection and correction of hypotension in the parturient reduces the occurrence and duration of severe hypotension during major regional blockade, a condition linked to the development of ASAS.[106,256] The differential diagnosis of neurological impairment following epidural anesthesia includes direct needle trauma, chemical myelopathies, symptomatic decompensation of coincidental tumors or vascular malformations, and infection.

Anesthetic considerations in anterior spinal artery syndrome

Women at risk include those with scleroderma, SLE, Takayasu giant cell arteritis, Raynaud syndrome, and atherosclerosis. Regional anesthesia is not contraindicated; however, avoidance of epinephrine-containing local anesthetic solutions would seem prudent. In addition, maintaining a normal mean arterial pressure for the duration of the regional technique is appropriate. For C/S in a woman with an *in-situ* labor epidural, bupivacaine rather than lidocaine with epinephrine would be reasonable. However, the risk of ASAS in this group must be extremely low and available information suggests that a necessary cofactor such as preexisting vascular disease or vascular malformation must be present. Effective management of ASAS emphasizes early diagnosis and treatment of any correctable factors. Pregnancy may cause increased susceptibility to impairment of spinal cord blood flow due to engorged venous plexi, which become more engorged during second stage pushing. Catheter-induced vasospasm may present with a clinical picture similar to ASAS and should be considered in the differential diagnosis. Appropriate management includes immediate withdrawal of the epidural catheter and neurological evaluation.

Summary

Diseases of the spinal cord in women in the childbearing years range from the very rare to the merely uncommon. Today, medically challenged patients are encouraged to integrate fully into society including the role of motherhood. For this reason, greater numbers of cord compromised patients will present for obstetrical anesthesia care in the future. Appropriate management decisions are based on an appreciation of the disease processes as well as the interaction between these processes and pregnancy. The

challenge is to achieve outcomes in these patients comparable to the general obstetrical population, and this is best achieved when care is provided in a cooperative setting. Providing care to these women is a tremendously gratifying experience.

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11 PERIPHERAL NEUROPATHY

Felicity Reynolds

Introduction

Peripheral neuropathy takes many forms and may occur as a primary condition or as a component of many diseases with multisystem manifestations. There are manifold etiologies: genetic, inflammatory, traumatic/compressive, metabolic, vasculitic, neoplastic, dietary, toxic/drug-induced. They may be classified as mononeuropathy, plexopathy, multifocal neuropathy (mononeuropathy multiplex), or polyneuropathy. They may affect primarily the cell body and/or the axon (neuropathy, axonopathy), or the myelin sheath (demyelinating neuropathy/neurapraxia).[1] As these categories are confused and confusing, and of little use to the anesthesiologist, a simple etiological classification is used here (Table 11.1).

Neuropathies may affect sensory, motor, or autonomic nerves, or a combination. Longer neurons are usually the most susceptible, so a predominantly distal distribution is common. Signs and symptoms may include muscle weakness and wasting, peripheral in onset, usually affecting the lower limbs first, with loss of tendon reflexes and sometimes with fasciculation, glove and stocking sensory loss, paresthesias, spontaneous pain, and autonomic dysfunction.[1]

Pregnancy may exacerbate some neuropathies, while pregnancy or parturition may be a direct or indirect cause of a variety of mononeuropathies and plexopathies,[2] many of which may be incorrectly attributed to neuraxial anesthesia.[3] Some peripheral neuropathies may alter drug sensitivity or impair respiration, and therefore present special challenges to the anesthesiologist. Pregnancy can also cause physical deterioration in restrictive respiratory disease, particularly if associated with scoliosis; it is important to remember that relief does not follow immediately after delivery, so the puerperium can be a dangerous time.[4,5]

Table 11.1 Classification of neuropathies

HEREDITARY/GENETIC NEUROPATHIES

- Hereditary sensory motor neuropathies (HSMN)
  - Charcot-Marie-Tooth disease (types I and II)
  - the X-linked form of HSMN
  - Dejerine-Sottas disease (type III)
  - Refsum disease (type IV)
- Hereditary neuropathy with liability to pressure palsy
- Familial dysautonomia
  - Riley-Day syndrome
  - Congenital deficiency of dopamine β-hydroxylase
  - (Shy-Drager syndrome)
- Neurofibromatosis types 1 and 2

INFLAMMATORY DEMYELATING POLYNEUROPATHIES

- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy

TRAUMATIC/COMPRESSIVE MONONEUROPATHIES AND PLEXOPATHIES

- Cranial nerve lesions (V, VI, VII, VIII)
- Upper limb neuropathies
  - Brachial plexus palsy
  - Radial nerve palsy
  - Carpal tunnel syndrome
- Lower limb neuropathies (obstetric palsies)
  - Lumbosacral plexus palsy
  - Femoral, obturator, sciatic, lateral femoral cutaneous (meralgia paresthetica), peroneal nerve palsies

NEUROPATHIES SECONDARY TO OTHER CONDITIONS

- Diabetes
- Porphyria
- Infection: leprosy, HIV, diphtheria
- Vasculitis
- Sarcoidosis
- Poisoning with heavy metals (lead, thallium, arsenic, mercury) and solvents
- Deficiency states
- Drug-induced neuropathies

These conditions are listed in the order in which they appear in the text

Hereditary/genetic neuropathies

Charcot-Marie-Tooth disease, also called peroneal muscular atrophy or hereditary sensorimotor neuropathy (HSMN) types I & II

This is an autosomal dominant genetic disease, but it can occur by mutation, so there may be no family history. It presents in childhood with difficulty walking, sometimes accompanied by pes cavus. There is weakness and wasting of the lower legs, foot drop, steppage gait, and reduced tendon reflexes, with later involvement of the hands and trunk, and variable distal sensory loss. The condition is slowly progressive. Type I is a diffuse demyelinating neuropathy presenting in the first decade. It is caused by a segmental duplication on chromosome 17p, which includes the

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gene for peripheral myelin protein. As with any cause of paralysis that may involve the trunk muscles during growth, there may be scoliosis and stunting, with impaired respiratory function. Type II is an axonal neuropathy; it presents later in life and is less severe.[1]

The condition, particularly the more severe type I, may be exacerbated in pregnancy.[6] The gravid uterus splints the diaphragm, so forced vital capacity (FVC) may fall and progressive respiratory compromise is well documented.[7,8] Paradoxically, however, a paralyzed abdominal wall may diminish respiratory embarrassment in pregnancy, as the abdomen and uterus can expand more easily, thereby reducing diaphragmatic splinting. Nevertheless, small stature is associated with premature labor.[5]

In a woman with severe Charcot-Marie-Tooth (CMT) disease type I, weighing 24 kg and with a 30° scoliosis and an FVC of 500 ml, requirement for mechanical ventilation increased during pregnancy from nocturnal only up to 22 hours a day, until she went into spontaneous labor at 30 weeks' gestation.[7] After cesarean section (C/S) under general anesthesia (GA) she was weaned gradually from daytime artificial ventilation without problems. If these needs are not anticipated, the sequence of events may be stormy. For example, a less severely disabled 100-kg parturient with CMT disease (presumably type II) who was not initially respirator-dependent, was also delivered by C/S under GA, but underwent numerous extubations and reintubations postpartum for 26 days until she was finally weaned.[8] There are many stories like this, some ending in disaster.[4] Orotracheal intubation is *not* suitable for weaning partially respirator-dependent patients, but neither is tracheostomy mandatory; a noninvasive form of ventilation such as a nasal mask, a mouthpiece, or, in the old days, an iron lung, can be tolerated without sedation and can therefore allow gradual or partial weaning, which is essential.[5,9]

For those severely affected with CMT disease type I, difficulty sleeping, increasing need to draw breath while speaking, and an FVC falling below one liter, may indicate the need for increased respiratory assistance during pregnancy.

There is no evidence of any sensitivity to malignant hyperthermia triggers, or abnormal sensitivity to succinylcholine in those with CMT disease,[10] but small scoliotic and paralyzed patients tolerate sedatives, respiratory depressants, and neuromuscular blocking (NMB) drugs poorly, and may die without respiratory support postoperatively.[4,5,10] Those who are orthopneic may equally be unable to tolerate the wedged supine position for awake C/S.[11] Though continuous spinal anesthesia has been used,[11] it may not be without problems, and GA with noninvasive respiratory support postpartum may be the best option for those with respiratory difficulties.[7] Patients who are already paralyzed require little extra muscle relaxation and less postoperative analgesia than normal.[12] It is essential to take account of body weight when estimating drug doses for GA and regional anesthesia.

Although access to the epidural space may be difficult if severe scoliosis is present, there is no apparent reason why less severely affected individuals should not be given epidural analgesia and undergo vaginal delivery.[5,13]

The x-linked form of HSMN is a rare sex-linked dominant disorder, similar to type 1, but female carriers are asymptomatic or only mildly affected.[14]

Dejerine-Sottas disease (HSMN type III)

This condition is similar to CMT disease, but usually recessive. It is slowly progressive with childhood onset, and may be characterized by enlargement of peripheral nerve trunks. There are no reported cases of pregnancy in mainstream literature, but a case was described in 1990 of a woman with this condition who had a $>90°$ scoliosis.[5] Her FVC fell during pregnancy from 950 to 400 ml at term and she suffered increasing respiratory failure with cor pulmonale. She was delivered by C/S at 33 weeks under GA and required noninvasive mechanical ventilation postpartum. This suggests that considerations for these patients should be similar to those with CMT disease.

Refsum disease (HSMN type IV)

This is a rare autosomal recessive condition characterized not only by a mixed motor and sensory neuropathy, usually distal, but also by ataxia, anosmia, pigmentary retinal degeneration, abnormal pupils, deafness, cardiomyopathy, and ichthyosis.[1] It presents in late childhood or early adult life, usually with night blindness, and is slowly progressive or relapsing. Peripheral nerves may become hypertrophic. It is due to an inability to metabolize dietary phytamic acid. It affects males and females equally.[15]

Mainstream literature contains no references to anesthesia or pregnancy in association with Refsum disease, but logically, anesthetic considerations must take account of possible impairment of cardiac function as well as respiratory insufficiency and peripheral neuropathy.

Hereditary neuropathy with liability to pressure palsies (HNPP)

This is an autosomal dominant disorder with variable penetrance that can present at any age. The cause is a deletion of the distal segment of chromosome 17p, which contains the gene for peripheral myelin protein,[16] the gene that is duplicated in CMT disease. The condition should therefore occur with the same frequency as CMT disease, but it must often go undiagnosed. There are recurrent focal peripheral nerve palsies particularly in areas that are susceptible to compression or stretch, such as the brachial plexus, the median nerve in the carpal tunnel, and the peroneal nerve.[1] Such nerve injuries lead to areas of local demyelination and cause episodes of numbness or weakness of varying duration.[16] Sausage-shaped swelling of myelin sheaths may be evident. The condition may exacerbate neuropathies associated with pregnancy and delivery, such as lumbosacral plexus, femoral, lateral femoral cutaneous, obturator or peroneal nerve palsies, more often than is appreciated.[17] Dense local anesthetic (LA) blockade should be avoided as it may mask a compression neuropathy. If a patient known to have this condition presents during pregnancy, Lepski and Alderson[16] suggest the following management principles:

- consult with a neurologist and anesthesiologist in the antenatal period
- assess neurological status antepartum

- avoid prolonged immobilization in labor
- avoid instrumental delivery
- avoid dense epidural blockade
- consider operative delivery if a pressure palsy develops in labor.

Then if C/S is selected, The HNPP website (www.hnpp.org) gives the following advice to the "surgical team":

- *Position arms out to sides*. An angle of less than 90° will help to alleviate stretch on the brachial plexus.
- *Move arms (supinate/pronate) every 15 minutes* under general anesthesia.
- *Pad arms and legs/feet* in stirrups. As a general rule: *PAD EVERYTHING*. The need to pad arms and legs is dependent upon the individual patient (frequency and severity of palsies). One inch foam or similar type material is usually sufficient.
- If possible *avoid leaning* against the patient, especially against the arms and legs.
- *Tape endotracheal tube* more centrally so that the tube is fully supported by the tape and not at all by the mouth. Tape other tubing in a similar manner as appropriate. Consider positioning while awake.

In order not to mask any developing neuropathy, anything but the mildest block for postoperative pain should be avoided.

Familial dysautonomia

One type of familial dysautonomia, Riley-Day syndrome, is a rare autosomal recessive genetic disorder found in Ashkenazi Jews, in which deficient norepinephrine stores impair the development of the autonomic and sensory nervous systems. It is characterized by autonomic instability (abnormal sweating, loss of vasomotor control, labile blood pressure) and sensory involvement (impaired taste with absence of fungiform papillae, diminished pain and temperature sensation, hyporeflexia) unexplained fever, vomiting attacks, impaired respiratory reflexes with frequent episodes of aspiration pneumonia, blunted responses to hypoxia and hypercarbia,[18] dry eyes and corneal anesthesia with ulceration. The symptoms are present from birth; short stature and scoliosis may become evident during growth.[1] Viable pregnancies with normal offspring have been described in women with Riley-Day syndrome.[19]

A rare type of dysautonomia is caused by congenital deficiency of dopamine β-hydroxylase, the enzyme that catalyzes the conversion of dopamine to norepinephrine. Neonates with dopamine β-hydroxylase deficiency have hypothermia, hypotension, and hypoglycemia.[20] Survivors have postural hypotension, as in the Riley-Day syndrome, but other features vary: nocturia, hypoprolactinemia, ptosis, hypermobile joints, high-arched palate, nasal stuffiness and occasionally abnormal behavior, sluggish reflexes, hypotonia, and raised blood urea.[21] Hypotension may be so severe as to provoke seizures.[20] There are reports of pregnancy in this condition, unlike the Riley-Day syndrome, and the course of pregnancy may be complicated. The condition has been treated successfully with dihydrophenylserine, which is converted by dopa decarboxylase to norepinephrine.[21]

Familial dysautonomia may be diagnosed by detecting a plasma norepinephrine/dopamine ratio of much less than one.[20] Because of chronic exposure to low levels of catecholamines there is supersensitivity to exogenous transmitter substances, but insensitivity to indirect acting vasopressors such as ephedrine. There are many important anesthetic considerations for labor and delivery in those suffering from dysautonomia, which are addressed below. Among childhood sufferers, ketamine has been reported to yield the least hemodynamic disturbance,[22] but epidural anesthesia has also been used successfully.[23]

Dysautonomia is more commonly encountered as a complication of diabetes than as a genetic condition (see later). The Shy-Drager syndrome as a cause of autonomic dysfunction does not normally affect women of childbearing age.

Anesthetic considerations for parturients with dysautonomia

A woman with dysautonomia is at greatly increased risk in pregnancy and parturition as she may have been suffering from repeated vomiting, she may have blunted respiratory responses, inability to compensate for intravascular volume depletion, and denervation supersensitivity. There may also be reduced respiratory reserve (see Charcot-Marie-Tooth disease).

During labor, and of course for C/S, histamine H_2-receptor blockers (e.g. ranitidine) and prokinetics (metoclopramide) are advocated for aspiration prophylaxis. Early recognition and treatment of fluid depletion can reduce hemodynamic instability. Inadequate analgesia may precipitate an autonomic crisis, while norepinephrine deficiency and an unpredictable response to vasopressors may complicate spinal or epidural anesthesia. One alternative is to use intrathecal opioids, with appropriate respiratory monitoring, for first stage pain relief, and pudendal or saddle block if necessary for second stage analgesia.

Cesarean section has been conducted successfully under cautiously titrated epidural anesthesia, combined spinal–epidural (CSE) anesthesia using a low dose of bupivacaine with fentanyl[20] and also local anesthesia.[24] For GA, doses of induction agents and inflation pressures should be kept to a minimum to avoid circulatory disturbance. Fluid lost must be scrupulously replaced, irrespective of the anesthetic technique. Direct arterial pressure monitoring and postoperative ventilation should be considered. *Small titrated doses* of direct-acting cardiovascular drugs such as phenylephrine (vasoconstrictor), isoproterenol (to increase heart rate), and esmolol (to decrease heart rate), rather than indirect acting agents, may be used to treat either sympathetic excess or deficiency. Sodium nitroprusside does not alter uterine blood flow or vascular resistance, but because of the possibility of fetal cyanide toxicity its use should be brief.

Modest narcotic analgesia, augmented by LA infiltration, may provide effective postoperative pain relief, as these patients have a reduced analgesic requirement.

Neurofibromatosis types 1 and 2 (NF1 and 2): see Chapter 8 for further details

These conditions affect both central and peripheral nervous systems. Both are autosomal dominant, but are caused by mutation in about 50% of cases. Nevertheless they are genetically distinct.

Both are characterized by a tendency to form tumors associated with nervous tissue and other organs.[25] Skin and peripheral nerve lesions are more common in NF1 (von Recklinghausen disease) and lesions in the central nervous system (CNS) in NF2 (also known as acoustic neurofibromatosis). The classical café-au-lait spots, together with freckling, are the hallmarks of NF1, while in NF2 acoustic neuromas are present in > 90% and skin plaques are common. The types and distribution of nervous system tumors and other organ involvement in the two conditions are described thoroughly by Huson[26] and by Hirsch *et al.*[25] Spinal deformities may be present in both conditions. NF1 has a prevalence of in the region of 1:5000 and is about 40 times commoner than NF2.[26] They are usually diagnosed in young adult life.

Pregnancy can stimulate tumor growth in both diseases. The most important anesthetic consideration is whether lesions in the spinal canal will interfere with neuraxial anesthesia, and whether neuraxial anesthesia will cause bleeding. While GA is often considered preferable for this reason,[27] the decision may be balanced if there is tumor involvement in the airway itself. Modern imaging within the CNS can allow accurate tumor localization, and judicious use of regional techniques has been described in selected cases.[28,29] Restrictive respiratory impairment, if present, requires particular attention (see Charcot-Marie-Tooth disease).

Inflammatory demyelating polyneuropathies

Guillain-Barré syndrome (acute inflammatory polyneuropathy)

Since the widespread use of poliomyelitis vaccination, Guillain-Barré syndrome (GBS) has become the commonest cause of acute paralysis, with an annual incidence of 0.6–2.4 cases per 100 000.[30] It is probably a collection of diseases, either axonal or demyelinating,[31] that may be idiopathic or triggered by various infections such as *Campylobacter jejuni*, Cytomegalovirus, Epstein-Barr virus, Mycoplasma, hepatitis B, human immunodeficiency virus (HIV), Chlamydia or even an upper respiratory tract infection or surgery.[1,32] It affects both sexes and all ages, but with peak incidences in young adults and the elderly, while pregnancy may predispose to it.

The condition develops over a few days to a few weeks, during which time the patient's condition may deteriorate rapidly. The first symptom is usually severe upper and lower back pain, followed by progressive symmetrical weakness starting in the legs and progressing to the trunk and sometimes the cranial nerves, with facial and bulbar weakness. There may be some sensory loss, but more commonly paresthesia of similar distribution. Dysautonomia is common, usually short lived, and may be manifest by sinus tachycardia or bradycardia, facial flushing, profuse or absent sweating, labile blood pressure, ileus and urinary retention. The cerebrospinal fluid protein is raised in the acute phase of the disease. The patient usually recovers within weeks or months. In 10–40% of cases there may be residual muscle weakness. Most mortality is due to autonomic instability, though respiratory and bulbar failure may contribute; the mortality rate therefore varies depending on the quality of care.

The presence of a gravid uterus increases the need for ventilatory assistance and exacerbates circulatory instability. Guillain-Barré syndrome is associated with an increased relapse rate and high maternal morbidity in pregnancy and the puerperium.[33,34,35] The outlook for the fetus is believed to be good, however, provided maternal physiology is well managed.

Management

It has been suggested that pregnancy does not alter the management of GBS,[36] and that GBS does not alter the process of pregnancy and labor, though these patients certainly require particular attention. It is vital to be on the lookout for, and treat promptly, both respiratory weakness and swallowing difficulty. Forced vital capacity should be monitored, since it is desirable to treat respiratory weakness *before* the blood gases are seriously disturbed. While noninvasive respiratory support has obvious advantages, the presence of bulbar weakness may necessitate tracheostomy in order to prevent aspiration pneumonitis, to provide safe mechanical ventilation and tracheobronchial suction. Circulatory support, attention to electrolyte balance and thromboprophylaxis are also needed.[36] Severe cases, including those in pregnancy, may be treated with plasma exchange and immunoglobulins, which attenuate the disease; steroids are useless.[37,38] Massive or repeated treatment with plasmapheresis or immunoglobulin is sometimes needed during pregnancy.[35,39] Where there is dysautonomia, plasmapheresis should be preceded by fluid loading.

Anesthetic considerations in parturition

Regional analgesia may be desirable in order to avoid exaggerated hemodynamic responses during labor.[40] Epidural[40,41,42,43] and CSE[35] techniques have been used successfully for both pain relief in labor and anesthesia for C/S. Sensitivity to regional blockade with LA is usually increased,[36,41] while hypotension and bradycardia may be excessive. Small gradually titrated doses of low-dose LA/opioid combinations are therefore advisable, with small doses of a direct-acting vasopressor if needed.[36] Responses to the latter drugs are erratic. If regional anesthesia is to be used for C/S, it is important to be on the lookout for respiratory compromise.

General anesthesia presents a problem in the parturient with GBS, since succinylcholine may cause dangerous hyperkalemia, even in the recovery phase of the disease.[36] Autonomic instability may provoke major hypotension from the induction agent. Sensitivity to all NMB agents is increased, while respiratory depressant drugs are also best avoided.[41] Bulbar weakness necessitates thorough antacid prophylaxis in order to mitigate the danger of aspiration during both induction *and recovery* from anesthesia.

Chronic inflammatory demyelinating polyneuropathy

Occasionally a condition that appears similar to GBS turns out to be chronic or relapsing, with widespread demyelination,[1] and is known as chronic inflammatory demyelinating polyneuropathy. The frequency of both onset and relapse, and of exacerbations of

the condition, is increased in pregnancy.[44] Relapse may occur during the latter half of pregnancy, sometimes postpartum and occasionally with the use of oral contraceptives. It may be treated with plasmapheresis or immunoglobulin, but, unlike GBS, the chronic condition also responds to corticosteroids.

The fetus and neonate are not affected by the disease itself. Obstetric and anesthetic management are similar to that for GBS.

Traumatic/compressive mononeuropathies and plexopathies

Most mononeuropathies and plexopathies that arise in pregnancy or parturition have a physical origin, but some, such as brachial plexus palsy, may have an inflammatory element.

Cranial nerve lesions

Idiopathic facial (VII) nerve palsy is about three times more common in pregnancy than in the nonpregnant population,[45] with most cases arising in the third trimester. It is probable that pregnancy increases the likelihood of compression of the nerve within the facial canal. It appears to be associated with pre-eclampsia, diabetes, migraine, and other cranial nerve palsies in pregnancy. On the affected side the sufferer is unable to wrinkle the brow, raise the eyebrow, close the eye, purse the lips, whistle, or smile.[46] There may also be dribbling and dysphagia; involvement of the chorda tympani branch may cause partial loss of taste in the tongue and altered lacrimal and salivary secretion.[47] Permanent dysfunction is unusual: recovery within the first three months postpartum is the norm. Treatment with prednisone has been successful with no apparent adverse effect on the parturient or fetus.

Involvement of the spinal nucleus of the trigeminal (V) cranial nerve in the cervical cord, causing transient facial weakness, has been reported in association with high epidural block during labor.[48,49] Because of the inverted representation of the fibers, the upper division is usually involved first, necessitating special care of the eye as the corneal reflex may be lost. Trigeminal, facial, abducent (VI) and VIII nerve palsies have all been caused by loss of cerebrospinal fluid following unintended dural puncture in parturients,[50,51] and even following puncture with a 25-gauge Sprotte needle.[52] The response of these palsies to epidural blood patch is not always encouraging.[53,54,55]

Upper limb neuropathies

Brachial plexus palsy is well recognized as a neonatal problem after difficult breech delivery, and may be seen in adults as a result of arm traction, cervical rib, neoplasm, and so on. An autosomal dominant familial inflammatory demyelinating form, however, may arise de novo or be exacerbated during pregnancy or postpartum in the mother.[56,57] Avoiding vaginal delivery has not been found to alleviate the problem.[56] The condition may be unilateral or bilateral, and is characterized by pain and weakness in the arm and shoulder girdle. The pain has been known to be so severe as to prompt one mother to request sterilization to avoid further pregnancy. This was followed by ectopic pregnancy, which provoked a further attack.[57] How unlucky can you get?

Radial nerve palsy. The radial nerve is vulnerable in the spiral groove at the midhumeral region. Radial neuropathy, resulting in upper arm weakness and commonly known as Saturday night palsy, has been described following prolonged use of a birthing bar.[58] Women should be instructed to rest the forearms rather than the upper arms on the bar.

Carpal tunnel syndrome resulting from compression of the median nerve beneath the flexor retinaculum at the wrist is a familiar problem during pregnancy.[46] Numbness, tingling, and burning sensations in the hand may radiate up the arm and are worse at night, often causing severe sleep disturbance. There may also be thenar wasting. The symptoms may be relieved by shaking the hand or otherwise keeping it moving. Although it usually resolves postpartum, it may arise de novo at this time (lactational carpal tunnel syndrome) and resolve only after weaning.

Obstetric palsies

In the past, when labor might continue for several days, and C/S, like anesthesia, was rare, obstetric palsies were well recognized. Several surveys in the years between 1935 and 1965 reported incidences around 1 in 2000 deliveries.[59,60,61,62] The classical syndrome, once termed traumatic neuritis of the puerperium, arose from pressure of the baby's head on the lumbosacral trunk as it crossed the pelvic brim.[46,63] The treatment was held to be bed rest, so the end result could be death from pulmonary embolus.[46]

The current incidence of postpartum neuropathy is difficult to determine as many surveys are too small to detect what has become a rare event, lack controls, and record irrelevant data.[64] Neuraxial anesthesia frequently gets the blame for many neurologic disorders,[3] although they are about five times more likely to result from obstetric factors.[65] Any form of anesthesia, signifying as it does a complicated labor, may be associated with an increased incidence of neurologic sequelae.[66] Transient neurapraxia involving the femoral, lateral femoral cutaneous, obturator, peroneal, and sciatic nerves can occur after vaginal delivery.[67,68] As in earlier days, nulliparity, prolonged second stage, prolonged lithotomy position, and assisted delivery, rather than neuraxial anesthesia, are associated factors.[68]

Root damage, usually mild and causing only paresthesia, may follow epidural analgesia, one survey detecting one case among 13 000 epidurals,[65] while the incidence following spinal anesthesia is probably tenfold higher.[69] Peripheral mononeuropathies may be the indirect result of neuraxial anesthesia if the resultant sensory loss allows nerve compression to go undetected.[70,71,72]

Many different mononeuropathies and plexopathies have been associated with pregnancy and delivery.

Lower limb neuropathies

Lumbosacral plexus injury is the commonest cause of postpartum foot drop.[73] The lumbosacral plexus is formed from L4 and 5 and sacral roots, but it is only the lumbosacral trunk (the union of the L4 and 5 roots) that crosses the pelvic brim where it is

maximally vulnerable to compression from the baby's head during labor. There may be sciatic-type pain during labor, with postpartum foot drop due to weakness of the anterior tibial and peroneal muscles, and paresthesias or numbness in the outer leg and foot, for months afterwards. There is sometimes gluteal involvement. The condition is occasionally bilateral. Sufferers are usually primiparous, have long labors, difficult vaginal deliveries, and large babies.[59,60,61,62] Recovery depends on how long the difficult labor is allowed to persist, but in one African community recovery was incomplete in 24% of women.[73] A history of this injury is a strong indication for C/S next time.

Femoral nerve palsy. Transient femoral neurapraxia is frequently detected after vaginal delivery, if sought.[67,68] The femoral nerve is vulnerable to stretching injury as it passes beneath the inguinal ligament; it may be damaged by prolonged flexion, abduction, or external rotation of the hip joint. Femoral neuropathy may follow prolonged adoption of an excessive lithotomy position,[74] and has been reported after difficult vaginal delivery.[75] Signs and symptoms are weakness of straight-leg raising, a diminished patella reflex, and numbness of the front of the thigh. Some hip flexion is present as function is preserved in the iliopsoas muscle; walking is therefore possible but mounting stairs is not. Clearly, prolonged use of extreme squatting and the lithotomy position during the second stage of labor are best avoided.

Obturator nerve palsy. The obturator nerve may be compressed both where it crosses the brim of the pelvis and within the obturator canal, so it would be expected to be vulnerable during difficult vaginal delivery.[1,46] Nevertheless, cases are rarely reported among parturients, suggesting the diagnosis may sometimes be missed. Three cases were detected when sought prospectively by Wong *et al*.[66] The mother may complain of pain when the damage occurs, and this is followed by weakness of hip adduction and internal rotation, with sensory disturbance over the upper inner thigh.

Meralgia paresthetica arises from compression of the lateral femoral cutaneous nerve as it passes between the two divisions at the lateral end of the inguinal ligament, where they attach to the anterior superior iliac spine. It is one of the most frequently encountered neuropathies in childbirth.[64,65,67,68] It may arise both during pregnancy, typically about the 30th week, and intrapartum, in association with rising intra-abdominal pressure. The presence of edema may contribute, as with the increased incidence during pregnancy of carpal tunnel syndrome and Bell's palsy.[47] It may recur during successive pregnancies.[76] Symptoms are unpleasant and include numbness, tingling, burning, or other paresthesias, affecting the anterolateral aspect of the thigh. The distribution is quite unlike that of a root lesion, yet when the condition is noted de novo postpartum, it is commonly attributed to neuraxial blockade by those unfamiliar with neuroanatomy. The symptoms can be expected to resolve following childbirth, but if they are severe during pregnancy, they may be relieved by local infiltration analgesia. In severe and persistent cases, surgical release of the nerve has been advocated.

Sciatic neuropathy has not generally been recognized as a complication of childbirth, possibly because it is mistaken for a lumbosacral palsy. It has, however, been described in four women delivered by C/S.[71,77,78] One woman who wished to attempt vaginal delivery with a breech presentation, was thin and was kept sitting in one position during labor while her leg numbness was wrongly attributed to epidural blockade. The second was obese and suffered a period of hypotension while lying on her right side during preparation for elective C/S under epidural anesthesia. Both experienced right-sided signs typical of sciatic palsy: absence of movement and loss of sensation below the knee, with sparing of the medial side. Motor changes recovered more quickly than the sensory changes, while occasional shooting pain recurred for some years.[71] Since that time two more cases of sciatic nerve damage have been described, in women who had C/S without hypotension and with a right hip wedge, who both suffered left-sided sciatic nerve palsy.[77,78]

Peroneal neuropathy results from compression of the common peroneal nerve as it winds round the head of the fibula. It may arise during labor as a result of incorrect and prolonged positioning in stirrups, or compression of the lateral side of the knee against any hard object. It may result from sustained knee flexion or prolonged squatting.[79] Signs of nerve compression may go unnoticed or be disregarded in the presence of regional blockade. The resulting foot drop may be profound, but plantar flexion and inversion at the ankle are preserved, unlike in an L4/5 lesion.[70] Sensory impairment spares the lateral border of the foot, which distinguishes it from sciatic nerve palsy.

Anesthetic implications

Neuraxial anesthesia or analgesia readily gets blamed for postpartum neurologic disorders,[3] so it is important firstly to be aware of any preexisting deficit, and secondly to make an accurate diagnosis of the site of the lesion. This need not necessarily involve expensive investigations such as conduction studies and imaging: it is often possible to distinguish between peripheral and central lesions by simple clinical means. For example, dermatomes (the spinal segments involved in the sensory supply to the skin) bear no relation to the peripheral nerve distribution to the skin (see Figure 11.1), while segmental motor supply also has a characteristic pattern (see Figure 11.2).

Anesthesiologists cannot wholly absolve themselves from responsibility for peripheral nerve injuries, if the dangers of stretch or compression under GA or regional anesthesia are overlooked. Moreover, among those with a hereditary liability to pressure palsy, even relatively brief periods of immobility or pressure on any one site must be avoided.

Neuropathies secondary to other conditions

Diabetes

Diabetes is the commonest cause of peripheral neuropathy and is present in about 15% of diabetics. It does not therefore qualify strictly speaking as an uncommon disorder. Any type or combination of neuropathies may be seen in diabetes, but two types predominate: (1) symmetrical combined sensory and autonomic neuropathy, and (2) mononeuropathy, single or multifocal.[1]

Diabetes requires meticulous attention during pregnancy for many reasons, and peripheral neuropathy, if present, can only

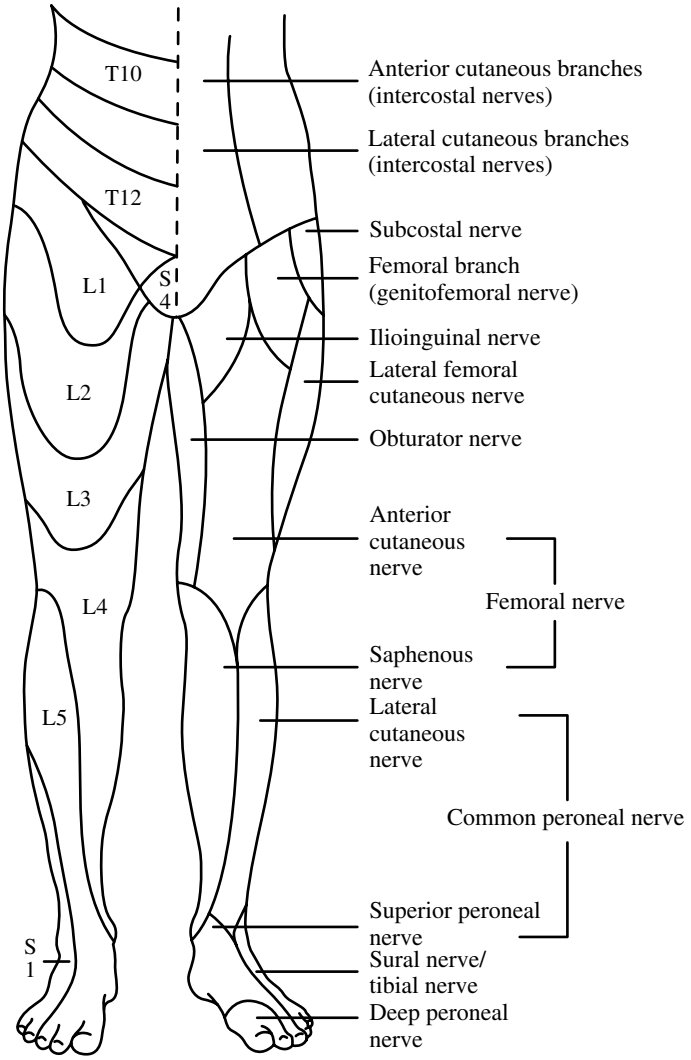

Figure 11.1 The segmental (right leg) and peripheral (left leg) sensory nerve distributions useful in distinguishing central from peripheral nerve injury. (From Redick, L. F. Maternal perinatal nerve palsies. *Postgrad. Obstet. Gynecol.* 1992; **12**: 1–6; by permission of the author and publisher.)

		L1	L2	L3	L4	L5	S1	S2	S3	S4
Hip	flexion	■	■	■	■					
	extension				■	■	■	■		
	abduction					■	■			
	adduction		■	■	■					
	medial rotation	■	■	■	■	■	■			
	lateral rotation					■	■	■		
Knee	flexion		■	■	■	■	■	■		
	extension		■	■	■					
Ankle	dorsiflexion				■	■				
	plantar flexion						■	■		
Big toe dorsiflexion					■	■	■			
Levator ani								■	■	■
Coccygeus										■

Figure 11.2 The spinal segments involved in the movements of joints in the leg. (Reproduced from Reynolds, F. & Bromage, P. Neurologic sequelae of childbirth and regional anesthesia. In Chestnut, D. (ed.), *Obstetric Anesthesia: Principles and Practice*, 3rd edn.), St Louis: Mosby, 2004, pp. 579–601[64]; by permission of the publisher. Data from Russell, R. Assessment of motor blockade during epidural analgesia in labour. *International Journal of Obstetric Anesthesia* 1992; **4:** 230–4.)

benefit from this. Diabetic autonomic neuropathy, however, is particularly dangerous in pregnancy.[80,81] It may be associated not only with postural hypotension and disordered baroreceptor reflexes, but also with diarrhea, gustatory sweating, bladder dysfunction,[82] and above all gastroparesis,[80] which may lead to severe intractable vomiting and electrolyte disturbance in pregnancy. Respiratory reflexes may also be impaired, leading to hypoventilation, while respiratory arrest has been described among diabetic women of childbearing age.[82] No wonder, then, that diabetic dysautonomia may be considered a relative contraindication to pregnancy.[80,81]

Nevertheless, in a prospective comparison of pregnant diabetic women with nonpregnant diabetics and nondiabetic pregnant women, Lapolla *et al.* found that pregnancy did not induce or worsen peripheral nerve dysfunction in insulin-dependent diabetes.[83] Diabetes was in all cases well controlled using home glucose monitoring and a team approach.

Management

Where there is a hint of peripheral neuropathy in a diabetic pregnant woman, autonomic function must be assessed. Heart rate variability in response to rising from lying to standing, to deep breathing, and coughing can demonstrate a < 5 beats/min rise, compared with the normal rise of > 15 beats/min.[81,82] Pupillary and lacrimal dysfunction, impaired sweating and vascular reflexes, postural hypotension, and atonicity of bowel and bladder also signify autonomic neuropathy.

In addition to the need for assiduous blood glucose control, the main factors that require consideration when contemplating anesthesia in the pregnant diabetic with a peripheral neuropathy are given earlier (see Anesthetic considerations for parturients with dysautonomia).

Epidural, spinal, or combined spinal–epidural anesthesia have all been recommended for both labor analgesia with vaginal delivery and C/S, and may be suitable provided low-dose LA/opioid combinations are used. Any procedure that might produce sudden hemodynamic changes should be avoided. Gastroparesis may be treated with metoclopramide.

Porphyria

Acute attacks in acute intermittent and variegated porphyria and coproporphyria may be accompanied by a predominantly motor neuropathy, but there may also be sensory and autonomic features. Facial paralysis, dysphagia, and ocular palsies are typical; the most severe cases may progress to respiratory paralysis. Mild cases regress in a few weeks, but severe cases and slowly progressing cases can leave a severe sensorimotor paralysis that takes months to improve. Pregnancy may provoke an attack.[84,85] The porphyrias are addressed fully in chapter 13.

Infection

Leprosy

With the ever-increasing use of air travel, leprosy has become a worldwide problem. It is a chronic infection of cool tissues and produces a multiple mononeuropathy that tends to affect superficial nerves,[86] particularly the median, ulnar, peroneal, and facial. Transmission is by direct contact or through respiratory mucosa, with low infectivity and a long incubation period of 3–5 years. The condition is slowly progressive, but periodically the immune system mounts a sudden massive and destructive increase in activity against *M. leprae*. Ultimately, nerve damage may become permanent. Lupus antibodies may be present. Dapsone, a folate antagonist, is the mainstay of therapy. It is inexpensive and is considered safe in pregnancy, but may provoke fever, leukopenia, anemia, and hemolysis and may itself cause a dose-related motor neuropathy; rifampicin and clofazimine are alternatives.

In women with leprosy, even though apparently cured, nerve function may deteriorate in pregnancy.[87] Relapse and exacerbation are maximal in late pregnancy. Fortunately the fetus is not infected.

A case is described in which CSE anesthesia was used successfully.[86] It is recommended that a patch of skin on the back that is not affected by the condition is selected for needle insertion.

Human immunodeficiency virus

Many types of peripheral neuropathy are seen in the HIV-infected patient.[88] They are caused by the infection itself, or by the rather toxic drugs that may be used in its treatment (see Table 11.2). The condition and its management are discussed more fully in chapter 18.

Diphtheria

This is now a rare cause of peripheral neuropathy. The exotoxin produces segmental demyelination. Palatal weakness may follow 2–3 weeks after pharyngeal diphtheria, and local muscle paralysis a similar interval after cutaneous diphtheria.[1] The condition may then spread to cranial nerves followed by generalized, predominantly motor, neuropathy. In severe cases the respiratory muscles may be affected.

Vasculitis

Peripheral nerve damage is encountered in many vasculitic syndromes (see Table 11.3)[89] and may be related to necrotizing angiitis of the vasa nervorum.[1] There may be a multifocal mononeuropathy, a distal sensory neuropathy sometimes restricted to the digitial nerves, or, in rheumatoid arthritis, an entrapment neuropathy. Most of these conditions are multisystem diseases that may interact with pregnancy.[90] (See Chapter 23.)

Sarcoidosis

Sarcoidosis is a rare cause of subacute or chronic asymmetrical polyneuropathy, which may be associated with polymyositis, or of mononeuropathy, often facial palsy. In some cases, multiple cranial nerves are affected successively.

Table 11.2 Peripheral nerve syndromes in HIV infection

Type	Comment
Distal symmetric polyneuropathy	Most commonly painful Etiology – cytomegalovirus – dideoxycytidine – dideoxyinosine – Vitamin B12 deficiency
Inflammatory demyelinating peripheral neuropathy	Similar to Guillain-Barré syndrome or chronic inflammatory demyelinating neuropathy
Mononeuritis multiplex	Associated with cytomegalovirus infection
Progressive polyradiculopathy	Associated with cytomegalovirus infection, CD4 < 50 Treat with ganciclovir
Autonomic	Treatment: fluid/electrolyte management; fluorocortisone; may require antiarrhythmic medication

Table 11.3 Some vasculitic neuropathies

Syndrome	Proportion with peripheral neuropathy
Polyarteritis nodosa	50–75%
Churg-Strauss disease	50%
Rheumatoid arthritis	1–5%
Systemic lupus erythematosus	10%
Wegener granulomatosis	20%

Pulmonary infiltration results in restrictive lung disease with a decreased vital capacity. Myocardial involvement may produce heart block, heart failure, paroxysmal dysrhythmias, and cor pulmonale. Uveitis, keratoconjunctivitis sicca, parotitis, hepatosplenomegaly, lupus pernio of the skin, and generalized lymphadenopathy also occur. Hypercalcemia develops in 10% of patients. Steroids are used to treat progressive lung disease and other serious manifestations.

Sarcoidosis is occasionally exacerbated by pregnancy. Obstetric and anesthetic management are dictated by the cardiopulmonary status of the mother.[91] Good maternal and fetal outcomes are possible in women with sarcoidosis.[92]

Poisoning with heavy metals and solvents

Heavy metals accumulate in the body and exert their toxic effects by combining with one or more of the reactive groups essential for physiological function.[93,94] They produce a variety of peripheral neuropathies (see Table 11.4). Exposure may come from high concentrations in soil or water, leaching from utensils and cookware, industry and mining, use of pesticides and therapeutic agents, burning fossil fuels containing heavy metals, and the addition of tetraethyl lead to gasoline.

Table 11.4 Poisoning with heavy metals

	Effects				
Substance	CNS	Peripheral nerve	Fetal	Other	Treatment
Lead	Mental retardation, headache	Motor (lead palsy) – wrist drop – foot drop – extraocular	Danger assumed	GIT Renal Hematological	Remove source Chelation (EDTA)
Thallium	Late convulsions and coma	Painful sensory followed by motor, ocular, and autonomic palsies		GIT dermatological	Prussian blue Mannitol Magnesium KCl ↑ renal excretion Thiocarbamate
Arsenic	Headache, confusion and convulsions	Sensorimotor neuropathy	Chromosomal breaks	GIT, hair loss, all organs	Sulfur, ipecac Gastric lavage CVS support Dimercaprol Penicillamine Hemodialysis
Mercury	Tremor, irritability, memory loss, etc.	Sensorimotor neuropathy	Cortical/cerebellar atrophy	Gingivitis, GIT Renal damage	Chelation (DMPS, DMSA, or EDTA)

GIT = gastrointestinal tract; KC1 = potassium chloride; CVS = cardiovascular system; CNS = central nervous system

Lead poisoning produces effects on the gastrointestinal, neuromuscular, central nervous, hematological, and renal systems. The neuromuscular syndrome (*lead palsy*) is now rare. The well-used muscles of the forearm, wrist, and fingers and extraocular muscles are commonly involved, more often those on the dominant side. Wrist drop and, to a lesser extent, foot drop are characteristic of lead poisoning. There is no sensory involvement. Evidence of permanent neurological sequelae from levels of lead previously thought safe raised fears of damage to the fetus and newborn, and led to the prohibition of organic lead-salt additives in gasoline and consumer products. Treatment of lead poisoning consists of removal from the source of exposure and administration of chelating agents (EDTA and penicillamine). Increased levels of lead in maternal blood have been associated with hypertension in pregnancy.[95]

Thallium is used as an insecticide and rodenticide, a catalyst in fireworks, in the manufacture of optical lenses, in industry as an alloy, and in cardiac perfusion imaging. Immediate symptoms of thallium toxicity are gastrointestinal with nervous system involvement (peripheral sensory, motor, and, less frequently, autonomic) beginning within a week of ingestion. Symptoms include paresthesias, myalgia, weakness, tremor, ataxia, and, less commonly, tachycardia, hypertension, and salivation. Treatment includes Prussian blue and mannitol or magnesium sulfate for gut decontamination, and potassium chloride (KCl) to enhance renal excretion. Avoid administration of systemic chelating agents, as they may worsen the neurologic symptoms.

Inorganic arsenic does not cross the blood–brain barrier, but does cross the placenta. It causes chromosomal breaks in cultured human leukocytes, and teratogenetic effects in hamsters. Manifestations of chronic arsenic poisoning include sensory and peripheral motor neuritis usually affecting the legs more than the arms. Acute treatment includes ipecac or gastric lavage, cardiovascular stabilization, dimercaprol, d-penicillamine, and hemodialysis, as indicated.

Mercury poisoning may produce a sensorimotor neuropathy similar to that caused by arsenic, although it primarily affects the CNS. Organic or methyl mercury is highly lipid soluble and readily crosses the blood–brain barrier and placenta and into breast milk. Elemental mercury is poorly absorbed by the gastrointestinal tract, but is readily absorbed as a vapor via the lungs. Inorganic mercury salts are absorbed through the gastrointestinal tract and skin. Prenatal poisoning produces cerebral palsy due to cortical and cerebellar atrophy. About 6% of American women have blood mercury concentrations above the safe reference level of 5.8 μg/l. Those intending to become pregnant should follow official advice about eating fish.[96]

A distal symmetric, predominantly sensory, axonopathy may follow exposure to certain hexacarbon industrial solvents such as n-hexane (in contact cement), methyl-n-butyl ketone (in plastic-coated and color-printed fabrics), dimethylaminopropionitrile (DMAPN) used in the manufacture of polyurethane foam, methyl bromide (fumigant), and ethylene oxide (gas sterilant).

Treatment of the multisystem disturbances, including peripheral neuropathy, associated with heavy metal and solvent poisoning is directed at life-threatening acute complications. Anesthetic management of the parturient is determined by the obstetric situation and degree of organic dysfunction present.

Deficiency states

In the Western world, nutritional polyneuropathy is usually associated with alcoholism. Mothers who have significant systemic

disease related to alcohol abuse are usually more than 30 years of age. A distal symmetric sensorimotor polyneuropathy occurs in alcoholics and is clinically indistinguishable from those due to diabetes mellitus, malnutrition, and HIV infection. Neuropathy in alcoholics may result from poor nutrition with deficiency of thiamine, pyridoxine, pantothenic acid, folic acid, or a combination of the B vitamins.[97]

The neuropathy has no effect on the course of pregnancy, but other alcohol-related organ dysfunction places the mother at increased risk. Alcohol abuse results in a myriad of acute and chronic complications, such as withdrawal seizures, aspiration pneumonitis, cardiomyopathy, liver dysfunction, peptic ulcer, malabsorption, pancreatitis, esophageal varices, coagulopathy, endocrine effects, and immunologic suppression.

The adverse fetal effects of alcohol have long been recognized. As well as the fetal alcohol syndrome, high rates of prematurity and infant mortality, and adverse perinatal outcomes have been linked to maternal alcohol abuse.

Obstetric and anesthetic considerations are not determined by the neuropathy although, as usual, the deficit must be documented. The presence of dysfunction in other organs should determine management. Coagulopathy may preclude regional anesthesia, while anxiety and acute intoxication may dictate GA. Nevertheless, general anesthesia may need to be modified to take account of the altered pharmacokinetics and pharmacodynamics associated with chronic alcoholism.

Drug-induced neuropathies

Many drugs are known to produce neuropathy (see Table 11.5). The major problem is diagnosis and, once it is established, further exposure must be avoided. Once the neurologic deficit is accurately documented, anesthetic options are governed by the obstetric, maternal, and fetal needs.

Table 11.5 Drug induced peripheral neuropathy

Drug	Effect
Isoniazid	Sensorimotor neuropathy; pyridoxine prevents
Pyridoxine	Sensory neuropathy (in large doses)
Nitrofurantoin	Sensorimotor neuropathy; also caused by uremia
Vincristine	Dose-related sensorimotor neuropathy; may develop foot drop
Cisplatin	Sensory neuropathy
Chloramphenicol	Mild sensory; optic neuropathy associated
Phenytoin	Mild sensorimotor neuropathy
Dapson	Motor neuropathy
Amiodarone	Sensorimotor neuropathy in 5%
Perhexiline	Sensory neuropathy
Metronidazole	Mild sensory neuropathy
Lithium	Sensorimotor neuropathy
Flecainide	Sensory neuropathy

Summary: general notes on management of parturients with peripheral neuropathies

Restrictive respiratory insufficiency

Causes

i. *Neuropathy affecting muscles of respiration*
- HSMN
- Guillain-Barré syndrome (GBS)
- Any neuropathy

ii. *Scoliosis*
- Conditions affecting trunk muscles during growth
- Typically HSMN (any type)

Signs
- Restlessness
- Difficulty sleeping, orthopnea, headache
- Tachycardia
- Breathless during speech
- FVC grossly reduced (FEV_1 is misleading when FVC is low)

Problems
- Pregnancy increases need for mechanical ventilation
- Sedation, anesthesia, and analgesia poorly tolerated
- Hypotension may produce cynanosis
- Anemia and blood loss poorly tolerated
- Neuraxial approach may be difficult
- Cannot lie flat for awake C/S

Management
- *Not* like obstructive respiratory insufficiency
- Noninvasive respiratory support may be needed sooner or later in pregnancy *and postpartum* if FVC < 1 L at outset
- Do not mistake tachycardia and cyanosis for a cardiac condition. Provide mechanical ventilation. Oxygen alone is not the answer
- Give GA if needed
- Requirement for NMB and analgesics are minimal
- Low threshold for blood replacement

Dysautonomia

Causes
- Diabetic neuropathy
- Hereditary dysautonomia
- GBS, etc.

Problems
- Hypoventilation due to impaired respiratory reflexes
- Vomiting and electrolyte disturbance
- Labile blood pressure, sensitive to positive pressure ventilation
- Sensitivity to direct-acting vasopressors
- Insensitivity to indirect vasopressors
- Oxytocin can be dangerous
- Both pain and GA may cause hemodynamic disturbance

Management
- Watch for hypoventilation
- Correct fluid and electrolyte balance

- Uterotonic in low divided doses
- Good pain relief using regional techniques with very low-dose combinations

Bulbar weakness

Causes
- GBS
- Any condition affecting relevant cranial nerves

Management
- Be on the lookout for it
- Metoclopramide
- Antacid and H_2 antagonist
- Care with intubation and recovery from anesthesia

Small stature, scoliosis

Causes
- Condition present during growth (typically HSMN)
- Scoliosis, skeletal disturbance

Problems
- Premature labor
- Malpresentation, distorted pelvis
- Neuraxial approach may be difficult. *Find old x-rays*

Management
- Remember weight when calculating dose for regional *or* general techniques. Do not be fooled into thinking that weight does not affect neuraxial dose requirement. It certainly does affect maximum safe dose.[98]

Neuraxial blockade and defensive medicine

It would be poor practice to avoid the use of regional techniques in the presence of a neuropathy, simply for fear of litigation. It is therefore wise to ensure that any preexisting neurologic deficit is fully mapped, and the patient understands that any exacerbation of her condition should not automatically be attributed to anesthesia. Remember it is much harder to produce chemical or irritative nerve damage in the epidural than in the subarachnoid space. Nevertheless, beware of concealing signs of nerve compression or attributing them to anesthesia.

Safeguards to minimize peripheral nerve compression

(Particularly important in those with HNPP, but see more precautions earlier under Hereditary neuropathy with liability to pressure palsies.)
- Watch for signs of nerve compression; do not automatically attribute them to regional blockade
- Avoid prolonged use of the lithotomy position, or else ensure that hip flexion and abduction are reduced to a minimum
- Avoid prolonged positioning that may cause compression of sciatic or peroneal nerves
- Use low-dose local anesthetic/opioid combinations during labor to minimize numbness and allow maximum mobility
- Use opioids, preferably on their own, for postoperative neuraxial analgesia, for the same reasons
- Ensure that those caring for women receiving low-dose combinations know that numbness or weakness should not occur, hence such symptoms should prompt a change of position.

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12 CHRONIC PAIN IN PREGNANCY

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Introduction

Pain is defined as a sensory and emotional experience associated with actual tissue damage or described in terms of such damage.[1] This definition has endured through time; however, the classification of the different types of pain is evolving. Original descriptions of pain were based on a temporal evolution, where the distinction between acute and chronic pain was that if it lasted for more than six months it was considered chronic. Another more conservative and innovative view proposed one month as the defining criterion.[2] These early definitions did not account for the mechanisms involved in the development of the pain. The prevailing contemporary view is to classify pain according to the primary pathology involved in the cause of pain, namely: inflammatory (acute) or neuropathic (chronic).[3] The latter can be considered a disease of the nervous system and not merely a symptom of some other condition.[4] Furthermore, poorly treated acute pain can lead to neuropathic chronic pain.[5] The current temporal cutoff value for chronic pain is three months.

During pregnancy, acute inflammatory pain, usually arising from labor and delivery, is the most common type of pain. However, other pain syndromes (chronic neuropathic or acute inflammatory evolving to chronic neuropathic) have been recognized throughout pregnancy. In this chapter we will discuss painful entities encountered during pregnancy, focusing on the chronic pain states and recurrent inflammatory pain that may lead to chronic pain.

Gender, pregnancy and antinociceptive pathways

Reviews of gender and pain have noted that the prevalence of most pain conditions appears to be higher in women.[6] This higher prevalence may be related to pain from sex-specific visceral organs, with the female pelvic region being more complex and the greater number of pathophysiological conditions directly or indirectly linked to female reproductive functions.[2] Much investigation has concentrated on somatic sensitivity; however, increasing knowledge about sex and hormonal differences has produced a better understanding about pain from pelvic organs.[7]

When sex differences are analyzed in terms of response to analgesic treatments, women respond better than men to opioid analgesia (both mu agonists and kappa agonists)[8] and cholinergic analgesia (mainly through the nicotinic component of cholinergic analgesia at the spinal level)[9] in normal and chronic pain subjects.[10] Men, in contrast, respond better to nonsteroidal anti-inflammatory drugs (NSAIDs).[8]

Gender and hormonal status are factors in antinociception during pregnancy.[11] Antinociception associated with pregnancy results from the interaction of circulating levels of progesterone and estrogen and the activation of two relatively minor opioid analgesic systems (delta and kappa) by the endogenous opioids dynorphin and enkephalin.[12,13] These opioids are felt to be quiescent under basal conditions. Modulation of these systems is controlled by descending noradrenergic pathways using stimulation of spinal α_2 receptors to amplify synergistically the antinociceptive response.[13] Benefits from this association are a decreased need of either agent to achieve a certain level of antinociception, coupled with the low likelihood of developing tolerance for each receptor type.[13] Even though the aforementioned mechanisms control some forms of pain during labor and delivery, breakthrough pain can still occur, depending on the magnitude or even the nature of the labor pain.

Several painful disease states are of particular interest during pregnancy due to their high prevalence, intensity of symptoms, and/or impact on daily activity. As maternal pain can potentially interfere with fetal development and growth[14] it is important to be aware of these conditions and to alleviate pain where possible to the benefit of mother and fetus. Headache, orthopedic problems, and fibromyalgia are more prevalent during pregnancy and so will be discussed in this chapter in addition to postpartum chronic pain.

Migraine

Migraine is a common disorder, with an overall prevalence greater in women than in men (18% vs. 6%), and the highest prevalence concentrated between the ages of 25 and 55 years, which are the most productive and reproductive years of life.[15] According to the World Health Organization, migraine is one of the most disabling chronic disorders.[16]

Migraine is the first category in the classification of headaches and it is further subdivided in two major subtypes: migraine with aura (MA) and migraine without aura (MO).[17] The prevalence of migraine during pregnancy is around 15 to 20%.[18,19] Retrospective studies,[19,20] and one prospective study,[18] found that in over 80% of cases MO improves during pregnancy (see Figure 12.1) while MA is less likely to improve.[20] These studies strongly support the role of estrogen as well as endogenous opioids, which progressively increase during pregnancy, in the genesis and modulation of migraine attacks.[18,21]

Pathophysiology

Migraine is a primary disorder of the brain, in which neural events cause dilation of blood vessels. This vasodilatation produces pain and further nerve activation, mainly through the ophthalmic

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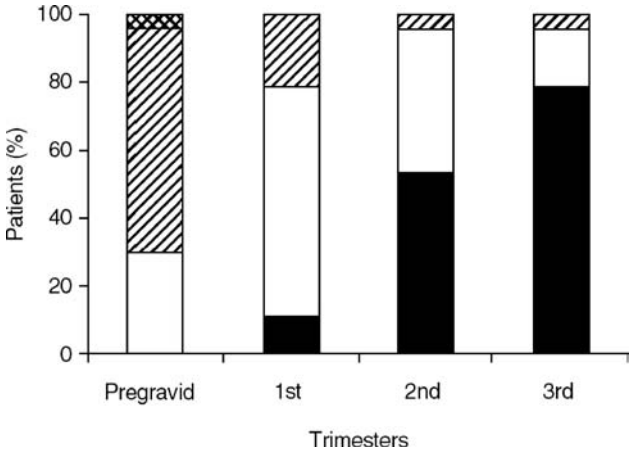

Figure 12.1 Attack frequency during the three months preceding pregnancy and during the trimesters of pregnancy in 47 women affected by migraine without aura. ■ = No attacks; □ = less than one attack/month; hatched = 1–3 attacks/month; double hatched = 1–3 attacks/week. First trimester vs. pregravid period, P = 0.0001; second vs. first trimester, P = 0.0001; third vs. second trimester, P = 0.02. Reprinted from Sances, G. *et al.*[18] with permission.

branch of the trigeminal nerve (see Figure 12.2).[22] This trigeminovascular system acts as a network extending in the walls of all major vessels and projects widely throughout the cortex, dura, and midbrain.[23] The originating event generating the neurovascular cascade that ends up in pain is unknown. However, evidence suggests that activation of trigeminal sensory neurons and release of mediators that modulate inflammation, vasodilatation, and extravasation of plasma proteins ultimately leads to pain.[15] Estrogen and other reproductive hormones interact with the trigeminovascular system, possibly explaining why headache can be influenced by pregnancy.[23]

Treatment

Behavioral interventions

Behavioral interventions may reduce analgesic drug requirements. As pregnant women are highly motivated to avoid medications this type of intervention is more likely to be acceptable during pregnancy. Three types of nonpharmacological interventions are frequently used: relaxation training, thermal biofeedback, and stress-management therapy.[24] Holroyd *et al.* compared a relaxation/biofeedback technique to propranolol therapy using a meta analysis. They found a 43% reduction in migraine headache activity in the study groups, with no improvement in controls (no therapy), and only a 14% improvement in the placebo group.[25] During pregnancy, Marcus *et al.* showed that relaxation coupled to thermal biofeedback provided a clinically significant improvement in headache activity in 73% of women compared to 29% in a control group.[26] Moreover, the beneficial effect of behavioral therapy is maintained in nearly two-thirds of women up to one year postpartum.[27]

Pharmacological interventions

Treatment of headache during pregnancy and the postpartum period is challenging, because few data are available about the risks of prophylactic or treatment medications.[21] Acetaminophen, a Food and Drug Administration (FDA) category B drug,[28] is commonly recommended for headache in pregnancy. Other FDA category B medications for headaches include NSAIDs, prednisone, and metoclopramide. Opioids, caffeine, and beta-blockers are FDA category C.[28] Recent trials addressing the usefulness and safety of sumatriptan (FDA category C) in pregnancy have yielded promising results with no evidence of untoward effects in the newborn.[29,30] Recommended drugs and dosages are depicted in Table 12.1.

Back pain

Back pain is one of the most common pain conditions in the general population, with a lifetime prevalence of 58–84% of all adults[6] and a peak at younger ages.[31] During pregnancy, the most common orthopedic complaint is backache, with a nine month prevalence close to 50%,[32,33] a stable point prevalence throughout pregnancy of 25%,[33] and a true incidence rate of 27%.[33]

Ostgaard *et al.* subdivided back pain into three categories: high back pain, low back pain, and sacroiliac pain.[33] This last group is referred to as posterior pelvic pain in some publications and seems to be closely related to the anterior or symphyseal pain,[33,34] which is discussed later in this chapter. This differentiation into three categories has prognostic value since posterior pelvic pain increases as pregnancy advances,[33] and it is more prevalent and more intense than back pain.[35] However, after delivery, posterior pelvic pain is usually less frequent and less intense than back pain.[35] Risk factors that have been consistently linked to back pain are: presence of back pain before pregnancy, multiparity, and heavy workload.[32,33,35]

Pathogenesis

During pregnancy there is increased ligamentous laxity,[36] thought to be due to hormonal influence (estrogen and relaxin).[37] Changes in the three-dimensional alignment of the normal spine as pregnancy progresses, coupled to normal weight gain, increase the mechanical strain on muscles, ligaments, and disc structures of the spinal column.[32] This leads to muscle fatigue and soft tissue strain, which generates pain.[32] When this derangement is severe enough to impair normal daily function because of pain or pelvic instability, it is referred to as symptom-giving pelvic girdle relaxation.[38] Differential diagnoses include lumbar disc herniation, spondylolisthesis,[39] and infectious sacroiliitis.[40]

Clinical symptoms

The usual complaint is posterior or low back pain, aggravated by activity and usually relieved by lying down or sitting. Often it is described as persistent and not very severe.[39] Patients can have complaints of pain above the lumbar region, in the lumbar region with or without radiation to the thighs or over the sacroiliac joint area, sometimes radiating to the buttocks and posterior thighs

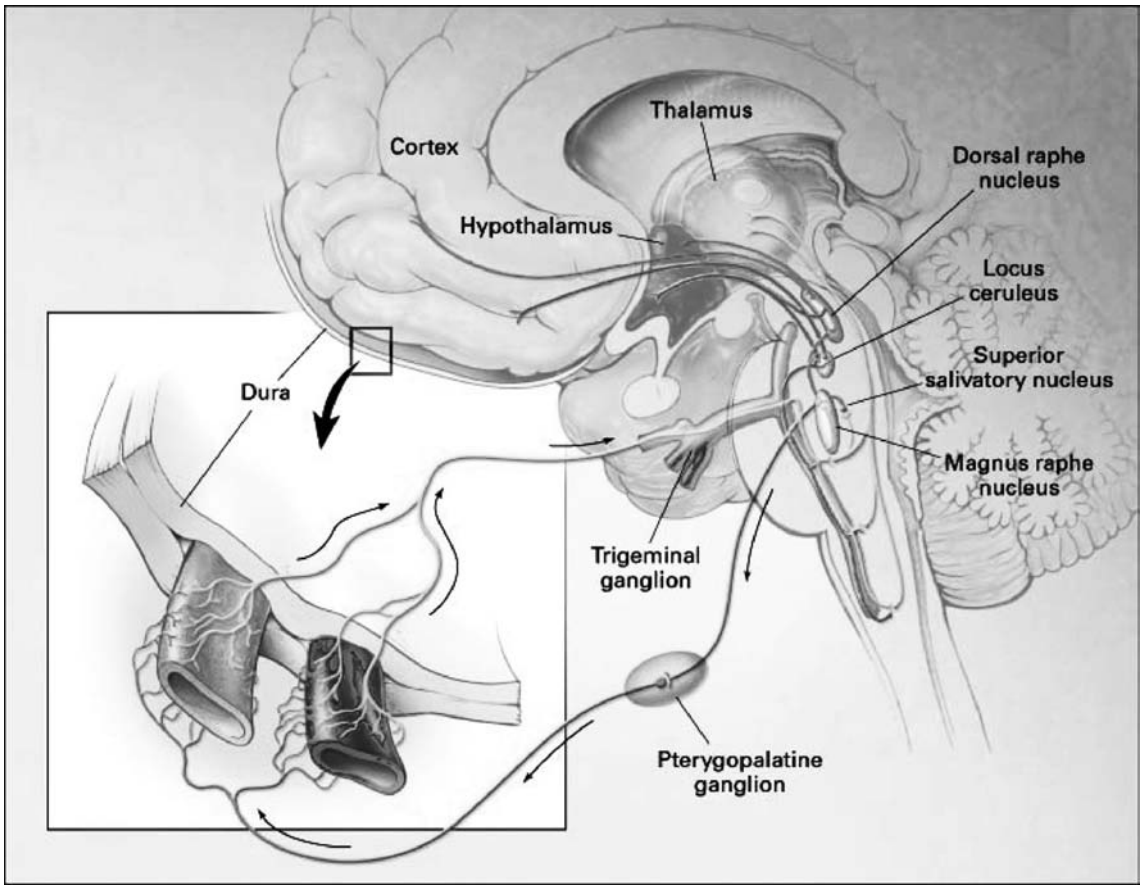

Figure 12.2 Pathophysiology of migraine. Migraine involves dysfunction of brain-stem pathways that normally modulate sensory input. The key pathways for the pain are the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex. These neurons, in turn, project through the quintothalamic tract, and after decussating in the brain stem, form synapses with neurons in the thalamus. There is a reflex connection between neurons in the pons in the superior salivatory nucleus, which results in a cranial parasympathetic outflow that is mediated through the pterygopalatine, otic, and carotid ganglia. This trigeminal-autonomic reflex is present in normal persons[34] and is expressed most strongly in patients with trigeminal-autonomic cephalgias, such as cluster headache and paroxysmal hemicrania; it may be active in migraine. Brain imaging studies suggest that important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus ceruleus, and nucleus raphe magnus. From Goadsby, P. J. *et al.*[22] with permission.

(but usually not in a sciatic distribution). This latter form is often accompanied by symphysis pubis pain.[33]

Treatment

The primary treatment is prevention. It has been suggested that good physical fitness prior to pregnancy reduces the risk of back pain in a subsequent pregnancy.[32,41] During pregnancy, once the acute pain subsides, an exercise program to increase spinal and abdominal muscle strength can help reduce the continued symptoms of back pain.[39] The main focus of treatment is to reduce the workload of the pelvic girdle and low back by reducing physical activity, avoiding stair climbing, and the use of extreme range of motion in the hips or the back.[35] In addition, the use of a nonelastic pelvic support reduces pain in more than 80% of women with posterior pelvic pain.[41] Drug therapy is usually restricted to acetaminophen and NSAIDs. Surgery is seldom required, unless a structural anomaly and neurological compromise is present.

Pubic pain

Some pregnant women experience severe pelvic pain in the pubic symphysis joint, which often worsens with subsequent pregnancies and may persist for years.[38] Prevalence rates of symphyseal pain with onset during pregnancy increases from 1.5% in week 12, to 6.4% in week 24, and 20.0% in week 36, while sacral pain is around 10% at the end of the first trimester, increasing and stabilizing at nearly 25% in the second and third trimesters.[34]

Ligamentous laxity occurs during pregnancy.[39] MacLennan *et al.* identified an association between high serum relaxin levels and pelvic pain associated with joint laxity during late pregnancy, with a prognostic correlation between relaxin levels and intensity of pain.[37] However, some patients may have high levels of circulating relaxin and be asymptomatic, suggesting that peripheral relaxin levels may not be as important as relaxin receptor levels,[37] or that there is no exclusive relationship between the hormone and the symptoms, as some have suggested.[36,42,43,44] What seems to be consistent is the relationship of symphyseal distention and pain.[45]

Table 12.1 Suggested drugs and dosages for prevention and treatment of headache during pregnancy.[15,22,54]

Preventive therapy	
Drug	Dose
Propranolol	40–120 mg q12h po
Metoprolol	100–200 mg qd po
Atenolol	25–100 mg qd po
Amitriptyline	10–75 mg qhs po
Treatment	
Drug	Dose
Acetaminophen	1 g q6h max po
Caffeine	100–200 mg po
	500 mg i.v.
Ibuprofen	400–800 mg q8h po
Naproxen	500–1000 mg q8h po
Sumatriptan	50–100 mg q12h po
	5–20 mg q12h nasal
	6 mg s.c.
Meperidine	25–100 mg q6h i.v.
Fentanyl	25–50 μg q6h i.v.

qhs = quaque hora somni; po = per os; qd = once a day
i.v. = intravenous; s.c. = subcutaneous

The symphysis pubis is a nonsynovial joint at the confluence of the pubic bones that is joined by intrapubic, fibrocartilagenous tissue.[46] Widening of the symphysis pubis can cause tenderness that is usually aggravated by exercise. Rupture of the symphysis pubis (diastasis pubis) is an uncommon event. However, there is a report of spontaneous pubic separation that was diagnosed after a laboring patient developed pubic pain under continuous epidural analgesia.[47]

Treatment

If separation is less than 1 cm, treatment is supportive with rest and conservative measures such as an ice pack. There may be some benefit from local anesthetic injections; however, their effect appears to be short lived.[48] For separations greater than 1 cm (criteria for diagnosis of pelvic instability),[45] treatment, such as reduction with tight pelvic binding, lateral decubitus position with absolute bed rest and NSAIDs, is indicated.[39,47] Surgical treatment may be considered in patients who have inadequate reduction, persistent symptoms, or recurrent diastasis.[47]

Carpal tunnel syndrome

Disregarding back pain, carpal tunnel syndrome (CTS) is the most frequent musculoskeletal complaint in pregnancy. Depending on the study design, definitions employed and sensitivity of the diagnostic tests applied in different series the incidence ranges up to 62%.[49,50,51,52] Neurophysiological evaluation reveals nerve dysfunction in nearly half of the women with clinical symptoms.[52]

Many authors consistently have reported a correlation between edema in pregnancy and CTS symptoms.[49,50,53,54] Padua *et al.* confirmed the correlation between edema and neurophysiologic behavior in CTS with the clinical finding of edema being diagnostic and predictive of CTS, as well as a marker of severity of symptoms.[52] Furthermore, it has been suggested that smoking and alcohol consumption may have a negative role in the development of CTS: probably due to impairment of the microcirculation of the hand, providing a negative contribution to the evolution of the syndrome.[52]

Prognosis

Approximately 50% of women will have persistence of symptoms one year postpartum; however, most report an improvement in their symptoms.[55] Patients with early onset of CTS symptoms as well as excessive weight gain during pregnancy are less likely to improve postpartum.[55] Some authors suggest that women with CTS during pregnancy have a higher risk of developing this condition later in life,[53] supporting the concept that poorly treated pain can lead to neuropathic chronic pain.[5]

Treatment

In identified cases, most clinicians are reluctant to recommend carpal tunnel decompression during pregnancy even when symptoms are severe,[56] since a high percentage of patients with CTS symptoms will resolve spontaneously after delivery. Thus, conservative measures are the mainstay of treatment during pregnancy.[57] Supportive and conservative therapies usually are indicated for patients who are sufficiently symptomatic. [53] Wrist splints placed on the dorsum of the hand, which keep the wrist in a neutral position and maximize the capacity of the carpal tunnel, often provide dramatic relief.[54] Wrist immobilization has been combined with dietary salt reduction, with excellent improvement in clinical and electrophysiological assessments.[57] Some authors advocate the use of hydrocortisone injections in the carpal tunnel, since over 65% of all CTS are derived from nonspecific synovial edema.[58] The benefits of other treatments (diuretics and NSAIDs) are, to date, inconclusive.

Surgical correction is recommended for patients with early onset of CTS, severe symptoms, or severe neurophysiologic impairment with deteriorating muscle tone and motor function despite conservative measures.[58]

Fibromyalgia

Fibromyalgia is a multisymptomatic syndrome defined by the core features of chronic widespread pain, exquisite tenderness at multiple anatomical sites, and other clinical manifestations such as severe fatigue, sleep disturbances, and associated symptoms related to visceral hyperalgesia (irritable bowel and bladder).[59,60] The overall prevalence is about 2–3%,[59,61] with a female predominance of approximately 8:1.[62] Fibromyalgia is more common in Caucasians and can occur in younger women at an age when they are more likely to be fertile.[59,61]

Although the pathophysiology underlying this syndrome is unknown, contemporary research has pointed to genetic factors,

combined with abnormal peripheral and central pain mechanisms (central sensitization).[59] Among factors associated with symptom onset are: infectious illnesses, physical or emotional trauma, and stress.[59]

On examination, patients with fibromyalgia have typical paired tender points. These exquisitely tender points are generally symmetric and are located at the occiput, trapezius, neck, anterior chest wall, epicondyle, low back, trochanteric region of the hips, and medial aspect of the knees bilaterally.[63] Other than these tender points, the remainder of the musculoskeletal examination in fibromyalgia is usually normal. There are no specific abnormal laboratory results associated with fibromyalgia, so diagnosis is established from the clinical features.[64] The diagnostic criteria are: (1) widespread pain for at least three months in combination with (2) pain on palpation at 11 or more of the 18 specific tender point sites.[65]

Fibromyalgia during pregnancy has not been well documented and few studies have focused on the natural history of fibromyalgia and pregnancy.[66,67] Ostensen *et al.* performed a prospective, observational study of 50 women allocated to one of two groups: women who had delivered a child while suffering from fibromyalgia or controls, who were women who had their children before the onset of fibromyalgia.[67] The symptoms reported by the first group (pregnant women with fibromyalgia) were generalized fatigue, back pain, muscle weakness, depression, and stiffness. These women also complained of aggravation of symptoms about one to three months postpartum and reduced capacity to look after their babies. Despite this, most women found pregnancy a positive experience. Those women who experienced multiple pregnancies did not describe any increase in the severity of symptoms in subsequent pregnancies, compared to the first one. Women with fibromyalgia gave birth to healthy, full term babies, with no difference in obstetrical outcome compared to the controls. Nearly all women described worsening symptoms of fibromyalgia during pregnancy, with the third trimester the worst, as well as increased functional impairment and disability postpartum.[67]

Treatment

Treatment of fibromyalgia involves a multimodal regimen that includes patient education, cognitive behavioral therapy, gentle exercise, and medications to help with sleep and pain,[68] plus antidepressants.[69] Although initial descriptions of outcomes after multimodal treatment were encouraging and optimistic,[66] recent reports suggest that this syndrome is often unresponsive to therapy[70] and has a poor prognosis.[69] With that in mind, the pharmacological management of pain in fibromyalgia should focus on the major sites of pain processing: namely peripheral pain generation, dorsal horn sensitization, psychological influences, and the descending pain pathways.[60]

There is no specific tissue pathology characteristic of fibromyalgia, at least in peripheral tissues. However, the central nervous system (CNS) is sensitized, so peripheral pain generators are not only perceived as being more painful but they also prolong and amplify the machinery of central sensitization. The most common pain generators in fibromyalgia patients are myofascial trigger points. These trigger points need to be identified and treated by stretching, improved physical conditioning, acupressure, and physician intervention with trigger point injections of local anesthetics[60] or local anesthetics mixed with corticosteroids.[69] Nonsteroidal anti-inflammatory drugs are usually ineffective for this condition.[71]

The modulation of central sensitization is mainly pharmacologic. Currently the only drugs approved by the FDA that modulate central reactivity are those that activate or amplify the descending pain pathways. These medications include tricyclic antidepressants, opioids, and α_2-adrenergic agonists.[60] Low-dose tricyclic antidepressants, such as amitriptyline 10 to 25 mg taken at bedtime, are generally considered the treatment of choice in fibromyalgia.[64] Tricyclic antidepressants are FDA pregnancy category C drugs (see Table 12.2) and are considered probably safe in

Table 12.2 FDA pregnancy categories

FDA pregnancy categories

Pregnancy category	Definition
A	Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits to treat serious disease in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Data from reference[28] and www.perinatology.com/exposures/Drugs/FDACategories.htm

pregnancy and lactation.[28] However, despite their widespread use only 25 to 30% of patients improve and the long-term efficacy is not sustained.[60,72] Opioids are used often in the treatment of fibromyalgia, but there have been no controlled clinical trials of their effectiveness. Opioids should not be the first analgesic choice, but they should not be withheld if less powerful analgesics have failed.[60] Tramadol, an FDA pregnancy category C drug,[28] is a weak opioid with a low side effect profile that has gained attention in the treatment of fibromyalgia. Initial trials using a single intravenous dose of tramadol 100 mg showed a 20% reduction in spontaneous pain compared to baseline and a 40% improvement over the placebo group.[73] In another study, the combination of tramadol and acetaminophen proved moderately effective, compared to placebo.[74] At present, there are no reports of tramadol treatment of fibromyalgia during pregnancy. α_2-Adrenergic agonists such as tizanidine (FDA pregnancy category C)[28] have been used successfully in some chronic pain disorders; however, there have been no controlled trials in fibromyalgia.[60] There is evidence, in the experimental setting, that blocking N-methyl D-aspartic acid (NMDA) receptors with ketamine[75] and/or dextromethorphan ameliorates pain in fibromyalgia subjects.[60]

Nonpharmacologic treatment

Multidisciplinary treatment of musculoskeletal disorders that includes physical rehabilitation and psychological, behavioral, and educational interventions has gained interest. [70,72] In addition to some evidence of efficacy, this treatment also demonstrates a cost-effective profile, which makes it plausible to be used for long-term treatment in the average patient. [70] Some studies suggest that a structured exercise program that emphasizes aerobic fitness training produces significant and sustained improvements in these patients,[59] while others have found no benefits from this approach.[69,76]

Pain in the postpartum period

Postpartum pain is often referred to as lower abdominal "after pains," which are perceived centrally in a recurrent fashion with an intensity that can be severe.[13] Murray *et al.* found that postpartum abdominal pain was greater in multiparous than primiparous women.[77] Holdcoft *et al.* confirmed that the intensity of "after pains" increased significantly with parity, and that parity also increased the number of pain sites.[78] This increase in pain with subsequent pregnancies supports the concept of plasticity whereby a previous painful event provokes changes in the chemical milieu in the spinal cord and triggers structural reorganization,[3] leading to an enhanced response on a subsequent painful insult.

Chronic postcesarean section pain

Persistent pain after surgery, also referred to as chronic postsurgical pain syndrome, is defined as the presence of pain that persists for more than three months after surgery, excluding the preoperative condition and other causes of pain.[79] The incidence of neuropathic chronic pain is known to be high after specific operations such as limb amputations, thoracotomies, and mastectomies, with incidences ranging from 5 to 80%.[79] However, little is known about the incidence after cesarean section. In a prospective observational study over a one-year period Nikolajsen *et al.* evaluated more than 200 patients who underwent cesarean section using a low transverse incision.[80] They found that pain lasted more than three months in 18.6% of patients, while 12.4% had persistent pain after ten months. Among patients with persistent pain, there was a greater proportion who had received general anesthesia compared to subarachnoid anesthesia for their procedure, suggesting a protective or preemptive role of neuraxial anesthesia in the development of chronic pain. This finding mimicked the results of two other studies of chronic pain following thoracotomy and prostatectomy.[81,82] It may be speculated that noxious input to the CNS is less during spinal anesthesia than during general anesthesia. Experimental and clinical studies have shown that an afferent barrage of noxious input can generate a central sensitization in second order noxious responding neurons and that such central sensitization may be associated with an increased risk of persistent pain.[80]

The severity of postoperative pain is a potent predictor of subsequent chronic pain;[5] however, this has not been well investigated. In a prospective study of 100 patients Lavand' homme *et al.* found a chronic pain incidence of 14.8% six months after cesarean section. Previous genitourinary tract infection and higher postoperative pain (characterized by wound hyperalgesia) were risk factors for developing chronic pain, probably in relation to central sensitization.[83] Finally, Luijendijk *et al.* found that the size of the surgical incision is strongly related to the risk of postoperative chronic pain, possibly due to nerve entrapment, neuroma formation, or skin numbness[84] (which can be interpreted as pain).

Treatment

Postoperative pain intensity and extent of tissue damage (including length of the surgical incision) are two of the factors that have been directly linked to postoperative chronic pain.[79] With this in mind, aggressive postoperative analgesia should be implemented as soon as possible, ideally in a preemptive fashion. However, this has not been found effective in the short term. Huffnagle *et al.* performed bilateral iliohypogastric-ilioinguinal blocks with local anesthetics prior to the surgical incision for cesarean section and found no benefit.[85] Others have shown encouraging good results by using multimodal preincisional treatment for hernia repair surgery. This treatment included systemic NSAIDs and NMDA inhibitors, ketamine, and local anesthetic infiltration of the incision site.[86] Others have shown that ketamine infiltration of the area of hyperalgesia around the incision reduced the incidence of residual pain up to six months after surgery.[87] This finding suggests that blocking the NMDA receptors is beneficial for long-term pain control, but also that the presence of hyperalgesia (a marker of central sensitization) could predict the development of persistent pain after surgery.[87] Therefore a preemptive effect is

most likely produced at the level of central sensitization rather than at a local site. Even if a preemptive mechanism is not demonstrated for ongoing pain control this approach is well supported from a humanitarian point of view.

As these patients are young women in charge of babies and young children, nonsystemic therapy is favored, whenever possible, in order to reduce the side effects related to systemic administration of analgesics and adjuvant drugs. Some authors recommend local infiltration of the scar,[48] especially at the most sensitive place (trigger point) with the long-acting local anesthetics bupivacaine or levobupivacaine 40 to 50 mg combined with methylprednisolone 40 mg and clonidine 50–75 μg. The patient is free to take acetaminophen and NSAIDs at home. This scheme can be repeated up to three times. If the pain is severe, the use of a strong analgesic such as tramadol can be used as first choice in combination with acetaminophen. Acetaminophen plus codeine is another option, leaving morphine as the last choice (Lavand' homme, personal communication, 2005).

Most of the time, the pain has a neuropathic component. If local infiltration is not successful, adjuvants can be added, such as antidepressants or anticonvulsants: the latter being more effective if the patient complains of a sensation of electric shocks. The antihyperalgesic effect of amitriptyline is obtained at a lower dose than the antidepressant effect,[88] so a dose of 25 mg (up to a maximum of 75 mg) at night is effective in this regard. Anticonvulsants such as gabapentin (100 mg up to 1800 mg per day) or pregabalin (75 mg up to 300 mg per day) can be added; however, many patients report side effects such as dizziness and nausea. Therefore, it is important to begin with a low dose of gabapentin and slowly increase it (Lavand' homme, personal communication, 2005). It seems likely that a multimodal approach to postoperative pain control is the most rational and effective option, with the added benefit of reducing individual drug dosages and side effects. Although regional analgesic techniques form the basis of postoperative pain management, current evidence indicates that combining them with NSAIDs is more effective.[89] Some studies have suggested that small doses of ketamine enhance opioid analgesia, prevent tolerance to opioids, and improve pain relief as well as reducing hyperalgesia.[79]

Uncommon chronic pain syndromes

Tarshis *et al.* reported a case of a pregnant patient with chronic pain secondary to *hereditary chronic pancreatitis* who was treated with spinal morphine 3 mg/day through an implanted intrathecal pump. When labor began, the patient's pain was very difficult to manage with intravenous drugs; however, after initiating epidural analgesia, pain management was optimal.[90] With increasing use of intrathecal opioids for nonmalignant pain, it is likely that the anesthesiologist will encounter these patients more frequently. Careful multidisciplinary planning can optimize pain management in the perioperative or peripartum period. Apparently, epidural analgesia can be used safely and effectively for labor analgesia in this population.

Pyke *et al.* reported a case of recurrence of *pregnancy-induced intercostal neuralgia*. The pain was related to stretching of the lower ribs and it interfered with daily living and night sleep. Injection of bupivacaine 0.5% and triamcinolone[48] completely relieved the pain. Others recommend epidural analgesia for pregnancy-induced intercostal neuralgia.[91]

Meralgia paresthetica is a symptom complex that includes numbness, paresthesiae, and pain in the anterolateral thigh.[92] The most likely etiology in pregnancy is entrapment of the lateral cutaneous nerve as it passes around the anterior superior iliac spine or through the inguinal ligament. Onset of symptoms, most commonly numbness on the anterolateral thigh, but possibly burning, tingling, and other paresthesiae, can occur at any time during pregnancy or immediately after labor and delivery. Symptoms, which are almost always self-limiting, can be disturbing to the parturient and may interfere with normal daily activities. The mother should be reassured that the symptoms usually resolve following delivery. Conservative therapy such as minimizing periods of standing, eliminating tight clothing, and using oral analgesics may contribute to recovery. As a last resort, surgical therapy is effective in some cases.[93]

Radiological examinations during pregnancy and the puerperium

Avoiding invasive procedures during pregnancy is one of the dictums that is still valid. Some radiological procedures are considered invasive as radiation may affect the fetus with the greatest fetal risk occurring between the eighth and fifteenth weeks of gestation. Irradiation at this time can result in a reduction in intelligence quotient (IQ), an increased risk of cancer in later life, an increased incidence of congenital abnormalities, and a possible increased genetic risk to the next generation.[94] Generally, this risk will be very small compared with the normal risks of pregnancy.[94]

Before a radioactive agent is administered to a mother who is breast-feeding, consideration should be given as to whether: (1) the test could reasonably be delayed until the mother has stopped breast-feeding; and (2) the most appropriate radiopharmaceutical has been chosen.[94]

Summary

Evidence suggests that inadequate relief of postoperative pain may result in harmful physiological and psychological consequences that lead to significant morbidity and mortality,[95] a delay in recovery, and a slower return to daily living. In addition, the presence of postoperative symptoms, including pain, significantly contribute to patient dissatisfaction with the anesthetic and surgical experience.[96] Most importantly, it has been recognized that inadequately treated postoperative pain may lead to chronic pain.[5] These factors have not been well evaluated in the obstetrical field, but recent research has shown that women at risk from more severe acute postcesarean pain can be predicted from various preoperative physical and psychological tests.[97] These tests, which include thermal pain thresholds and the State Trait and Anxiety Inventory, have yet to be used to determine who is likely to develop chronic pain. However, it is

reasonable to conclude that pain states both during and after pregnancy should be promptly and effectively treated. It is possible that such treatment will have long-term benefits for the fetus, offspring, and the mother: a result of reducing various physiologic stresses and psychological distress. Finally, recent studies of the neural changes and their regulation, associated with incisional pain, are improving our understanding of the pathophysiology of acute and chronic pain states. For example, one study has shown an upregulation of prostaglandin E_2 and interleukin 6 at central sites to be an important component of surgery-induced inflammatory responses, which may influence clinical outcomes.[98]

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13 DISORDERS OF INTERMEDIARY METABOLISM

Stephen Halpern and Bhadresh Shah

Introduction

There are a large number of inherited conditions that result from disorders of intermediary metabolism. These cause symptoms because of the build up of precursors, the absence of the final product, an excess of toxic intermediaries, or a combination of these mechanisms. Many are fatal in childhood, but some are compatible with adult life and pregnancy. These disorders may be encountered by an obstetric anesthesiologist (either because of their prevalence or, for some rare conditions, because modern management confers an improved chance of fertility). Some examples of these disorders can be found in Table 13.1. Malignant hyperthermia, plasma pseudocholinesterase deficiency, and inherited hematological, endocrine, connective tissue, or bone disorders are discussed elsewhere.

In all these rare disorders, a basic tenet of management is to refer to a specialist in the relevant field of medicine, to coordinate a multidisciplinary team approach and to make a thorough and early antenatal assessment, with documentation of a plan of management.

Glycogen storage diseases

Glucose metabolism plays a fundamental role in supplying energy for most cellular metabolic processes. Glycogen, the storage form of glucose, is composed of a branched polymer of glucose residues and can be found in muscle and liver. Defects in glycogen metabolism typically cause accumulation of glycogen in the tissues.[1] Historically, the glycogen storage diseases have been classified numerically according to the specific enzyme defect. Since the main manifestations are either primarily related to liver or muscle, it may be more useful to categorize them according to the primary organ involved. Unlike some disorders of lipid metabolism, many of these disorders are responsive to dietary therapy.

Pompe disease or Cori type II glycogen storage disease is one of a group of genetic disorders involving pathways for the synthesis, storage, and utilization of glycogen. Those enzyme deficiencies related to liver conversion of glycogen to glucose are classified *hepatic-hypoglycemic* forms, and those related to muscle conversion of glycogen to lactate form the *muscle-energy* group. Pompe disease, one of the latter, is a deficiency of α-glucosidase and has an incidence of about 1 in 100 000.[1] It is often misdiagnosed as muscular dystrophy although a specific biochemical test is available to help differentiate the two. Cardiomyopathy is not a feature of the disease. Weakness, fatigue, and muscle cramps and back pain are common initial complaints. Patients may become debilitated and require walking aids or a wheelchair in early adult life. Some require respiratory support for at least part of the day.[2] Obstructive sleep apnea may also be present.[3] Thus, careful preoperative assessment of respiratory function, including arterial blood gas analysis and pulmonary function testing, is necessary before deciding on anesthetic management for surgery during pregnancy. Specific enzyme replacement therapy may be beneficial[4] when it becomes widely available. Currently, there are no case reports of parturients with Pompe disease.

McArdle disease or Cori type V is a rare autosomal recessive hereditary myopathy due to a deficiency of glycogen myophosphorylase, which is required for the conversion of glycogen to lactate during anerobic exercise.

Although more prevalent in males, affected females are otherwise healthy and, as fertility is unaffected, pregnancy is likely. The accumulation of glycogen in skeletal muscle produces symptoms of muscle fatigue and cramping during exercise. The diagnosis is usually made in early adulthood and affected individuals, who may find exercise levels at which they remain asymptomatic, lead a normal existence. Symptoms can be reduced by glucose or fructose ingestion before exercise. A history of myoglobinuria is usually present after heavy exercise, but rarely precipitates acute renal failure. The myocardium and myometrium are usually unaffected, although one case with an abnormal cardiac conduction pathway[5] and another with a familial cardiomyopathy have been reported.[6] The liver is normal and muscle wasting is uncommon, except in older patients who may exhibit upper limb wasting. Diagnosis is based on assay of serum lactate (with failure to rise), pyruvate, muscle enzymes, and myoglobin during ischemic exercise testing. Confirmation is by muscle biopsy and genetic studies.

Obstetric and anesthetic implications

Pregnancy in women with McArdle disease has been described and appears relatively uneventful.[7] Regional anesthesia likely confers its usual advantages. Successful, uneventful epidural anesthesia for cesarean section (C/S) and postoperative analgesia has been reported in the first pregnancy of a woman with McArdle disease.[6] General anesthesia for C/S has also been described in the same woman.[6] On theoretical grounds, succinylcholine should be avoided due to the risk of myoglobinemia, myoglobinuria, and possible renal failure. Response to nondepolarizing muscle relaxants appears to be normal.[6,7] A modified rapid sequence induction using a nondepolarizing drug, with monitoring of neuromuscular block, would seem appropriate. Rocuronium is probably the preferred agent, because of its rapid onset and intermediate duration, although atracurium

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Table 13.1 Examples of metabolic diseases caused by intermediary metabolic defects

Category		Examples	Key features	Obstetric and anesthetic implications
Lysosomal storage diseases		Gaucher	Liver and spleen enlargement; thrombocytopenia; pulmonary abnormalities; skeletal deformities.	Anticipate postpartum hemorrhage; thrombocytopenia; platelet function defect; pulmonary hypertension.
Glycogen storage diseases	Liver	Von Gierke; Forbes; Cori I and III	Growth retardation; enlarged liver and kidneys; hypoglycemia; elevated blood lactate, cholesterol, triglycerides and uric acid; bleeding diathesis.	Successful pregnancies have been reported. Avoid hypoglycemia. Coagulation screen.
	Muscle	McArdle; Pompe; Tarui	Exercise intolerance; muscle cramps; myoglobinuria.	Theoretical contraindication to succinylcholine. Minimize shivering. Perioperative blood glucose control. Frequent use of noninvasive blood pressure cuff measurements may lead to muscle cramping (see text).
Disorders of amino acid metabolism	Phenylalanine	Phenylketonuria	Mental retardation (if not treated in the neonatal period).	No anesthetic implications. Diet control is important for neonatal outcome.
Homocystine		Homocystinuria	Marfanoid features; lens dislocation; mental retardation; skeletal abnormalities.	Thrombosis. Pregnancies complicated by preeclampsia.

was used in the case cited above. While there is no known link between McArdle disease and malignant hyperthermia, some patients may have a positive in vitro contracture test.[8] While these authors suggest that potent inhalational agents, neuroleptics, and sympathomimetic agents (such as ketamine) be avoided, there is currently insufficient information to endorse these recommendations. The risk of compromised postoperative respiratory function secondary to myopathy is low in the reproductive age group.

The use of tourniquets or frequent repeated noninvasive blood pressure (BP) recordings is inadvisable since repeated use of an automated BP device has precipitated muscle cramps.[7] The use of a manual BP cuff may reduce tourniquet time. Alternatively, an arterial line may be used if there is a specific need for tight BP control. Pyrexia, hypothermia, and shivering should all be avoided because of poor temperature compensatory mechanisms and the risk of myoglobinemia with severe shivering. The perioperative administration of intravenous (i.v.) dextrose as a substrate has also been recommended, but requires titration to maintain normoglycemia, since the fetal and neonatal consequences of maternal hyperglycemia must be considered.

Cori disease (type III), also known as Forbes disease or Debrancher enzyme deficiency is a rare *hepatic-hypoglycemic* form of glycogen storage disease, which in mild cases may first present in adulthood with a myopathy similar to McArdle disease.[1] Important additional anesthetic considerations are the high risk of hypoglycemia with fasting, and the presence of cardiac myopathy. In severe cases, hypoglycemia must be prevented in order to preserve pregnancy.[9]

Pregnancy in patients with von Gierke disease (Cori type Ia) has been described but is rare. The main challenge is to maintain euglycemia. This is often accomplished with supplementary cornstarch feeding.[10] Pregnancy has also been described following combined renal-hepatic transplantation in a woman with von Gierke disease.

Tarui disease (Cori type VII) is caused by phosphofructokinase deficiency. The disease is phenotypically similar to McArdle disease and Forbes disease since patients suffer from clinically significant muscle weakness. To date there are no clinical reports of this disease associated with pregnancy.

Tarui disease can present as acute renal failure and hemolytic anemia in affected women of childbearing age. This may be the result of rhabdomyolysis following strenuous exercise. Diagnosis can be confirmed by ^{31}P-magnetic resonance spectroscopy.[11]

Lysosomal storage disorders

Lysosomes are cytoplasmic organelles, which enclose an acid environment and contain enzymes that hydrolyze macromolecules. The diseases discussed involve mainly single gene defects affecting one or more lysosomal enzymes, leading to accumulation of substrate. Most are inherited as autosomal recessive disorders.[12]

Gaucher disease

Gaucher disease, the most common sphingolipidosis, is caused by deficiency of the lysosomal enzyme glucocerebrosidase. Adult

Gaucher disease is one of three forms of Gaucher disease. It is marked by absence of neurological involvement by virtue of the presence of the common 1226G (N370S) mutation. It is especially prevalent among the Ashkenazi Jewish population, with a disease frequency of about 1:850 live births. It is present in other ethnic groups with a disease frequency between 1:40 000 to 1:60 000 in the general population.[13] There is tremendous heterogeneity in the severity of clinical manifestations of type I disease, ranging from asymptomatic to patients who experience lifelong debilitating disease.

Most patients present with enlargement of the spleen and liver, thrombocytopenia, and anemia. In some, splenectomy is required because of the size of the spleen and to reduce the severity of thrombocytopenia. Liver function tests are rarely affected. Platelet function defects, unrelated to absolute numbers of platelets, may be more common than previously appreciated with 22% of patients having defects in platelet aggregation, response to ADP, collagen, and/or epinephrine.[14] Skeletal involvement may include osteopenia, avascular necrosis of the large joints, pathological fractures, and lytic lesions. Visceral involvement may include lung parenchymal disease, abnormal pulmonary function, and in severe cases, pulmonary hypertension.

Obstetric implications

Enzyme replacement therapy (which is very expensive – $21 000 per infusion) has improved pregnancy outcomes by reducing the incidence of spontaneous abortions and by allowing women who have been more severely affected (as measured by standardized scoring) to become pregnant.[15,16] The placental enzyme alglucerase is being replaced in some centers by the recombinant enzyme imiglucerase because it is more cost effective. However, imiglucerase has been known to cause anaphylactoid reactions.

Skeletal deformities may affect the pelvis and hips leading to a higher incidence of C/S, although vaginal delivery, with careful positioning, may be possible.[17] The effect of pregnancy is variable. Some women experience improvement, though more frequently those mildly affected show no change, but some experience worsening hematologic parameters. Postpartum hemorrhage requiring transfusion occurred in 5 of 16 pregnancies in one series.[15] This may have been caused by thrombocytopenia or a defect in platelet function.

Anesthetic implications

A published report of eleven women with Gaucher disease described a total of seven C/S and nine vaginal deliveries.[18] Maternal thrombocytopenia was common. There were eight pregnancies in which the platelet count was $<100\,000/mm^3$. The lowest count was $27\,000/mm^3$. Only one woman received a general anesthetic for C/S (platelet count $72\,000/mm^3$). The remainder ($n=6$) received a spinal anesthetic. One woman received i.v. patient-controlled analgesia for labor for the same indication (platelet count $27\,000/mm^3$). Of note, three women received a regional block with platelet counts between 66 000 and 75 000/mm^3. While this small series does not prove that regional anesthesia is safe, it may be considered in the absence of other laboratory evidence of coagulopathy or history of abnormal bleeding.

Pulmonary involvement in Gaucher disease may be life threatening. Although it usually correlates with disease severity, enzyme replacement therapy does not seem to relieve symptoms. Some authors have recommended that patients on enzyme replacement therapy should have an echocardiogram to assess the severity of pulmonary hypertension.[19]

Mucolipidoses II

Mucolipidoses II is a rare disorder presenting with progressive skeletal deformities from the first decade and mild mental retardation. Survival to adult life is common in females.[12] Its specific importance to the anesthesiologist lies in the likelihood of aortic and mitral valvular disease. To date, there have been no reported cases during pregnancy.

Disorders of amino acid metabolism and storage

Phenylketonuria

Phenylketonuria (PKU) has an incidence of 1 in 10 000, making it one of the more common disorders of amino acid metabolism, which collectively occurs in about 1 in 1000 live births.[20] Phenylketonuria is due to reduced activity of liver phenylalanine hydroxylase, an enzyme that converts phenylalanine to tyrosine, leading to accumulation of phenylalanine and its precursor phenylpyruvic acid in the blood, urine, and tissues. This results in early mental retardation unless dietary treatment is instituted immediately after birth (elimination of dietary proteins and substitution with an artificial amino acid mixture very low in phenylalanine). With neonatal screening (the Guthrie test) and early detection, plus continued childhood dietary control, many affected women have reached childbearing age free of mental handicap.

Obstetric and anesthetic implications of PKU

Although fetal outcome is not affected by the inheritance of PKU, the presence of elevated maternal phenylalanine, and subsequent fetal accumulation, causes serious damage in the normal (nonPKU) fetus. In a recent report from France, 79 patients and 135 pregnancies were studied.[21] This report showed that pregnancy outcomes improved as patients gained access to information concerning appropriate diet and pregnancy planning. Effects of maternal PKU on the fetus and newborn include facial dysmorphism, microcephaly, IUGR, developmental delay, and congenital heart disease. A phenylalanine restricted diet should preferably start before conception to avoid fetal anomalies.[22] Cardiac defects were found only in infants exposed in utero to unrestricted diets.[21] To date, there are no case reports of anesthesia for this condition during pregnancy. It seems unlikely that any specific modifications to management would be necessary on the basis of mild hyperphenylalaninemia alone (i.e. serum level $< 600\,\mu M/l$).

Table 13.2 Clinical manifestations of acute porphyria

Site	Manifestation
Autonomic neuropathy	Abdominal pain
	Tachycardia
	Hypertension
	Constipation
	Vomiting
	Abnormal sphincter function
	Diarrhea
	Cardiac dysrhythmia
Peripheral central or motor neuropathy	Back and extremity pain
	Numbness of hands and/or feet
	Muscle weakness
	Respiratory muscle paralysis
	Pneumonia
	Cranial nerve neuropathy
	Bulbar
	Facial weakness
Central nervous system	Mental changes
	Insomnia
	Anxiety
	Depression
	Hallucinations
	Convulsions (may be multifactorial)
	Decreased level of consciousness
	Extensor plantar signs
Metabolic changes	Dark/red urine
	Hyponatremia
	Liver dysfunction

Homocystinuria

Homocystinuria, due to cystathionine β-synthase deficiency, is the most common of seven distinct disorders (incidence 1 in 200 000) of homocystine metabolism. Increased plasma levels of homocystine and methionine, and decreased cystine lead to manifestations such as mental retardation, seizures, dislocated optic lens, osteoporosis, and thromboembolism. Pathophysiology is secondary to the interference of homocystine in cross linking of collagen and increased platelet adhesiveness. Early diagnosis and treatment of homocystinuria with pyridoxine, plus methionine restriction, allow a benign clinical course.[20] Pyridoxine-nonresponsive homocystinuria can be treated with betaine, which serves as a methyl donor in a reaction converting homocysteine to methionine.[23] Successful pregnancies in women with pyridoxine nonresponsive homocystinuria have been described after treatment with betaine and anticoagulants.[24,25]

Obstetric and anesthetic implications of homocystinuria

An international review of homocystinuria identified 108 pregnancies among 47 affected women, mainly those who had responded to pyridoxine and had higher intelligence.[26] Pregnancy loss was very high in a small number of heterozygote mothers. In these situations the fetus was exposed to modest elevations of homocystine.[27] Thromboembolism is a major concern and cerebrovascular disease has been reported.[28] Since normal pregnancy causes a hypercoagulable state, these women may require prophylactic anticoagulation antenatally (for example subcutaneous unfractionated heparin [UFH] or low molecular weight heparin [LMWH]), with continued therapy following delivery.[28] The obstetric anesthesiologist should see these women in consultation and, in conjunction with the obstetric and medical teams, formulate a management plan that preserves the option of regional analgesia and anesthesia. This may mean stopping LMWH when labor starts or changing to UFH at 38 weeks' gestation. Communication among caregivers is necessary to determine the optimum time to discontinue prophylactic anticoagulation before delivery.

The porphyrias

The porphyrias are a group of seven metabolic disorders associated with specific enzyme defects in the heme synthetic pathway that result in overproduction of porphyrins and subsequent clinical signs and symptoms (see Table 13.2). [29] All are inherited, although porphyria cutanea tarda (PCT) may be acquired as a result of reversible uroporphyrinogen decarboxylase inhibition, secondary to exposure to environmental toxins such as lead or certain fungicides.[30] The defect may occur at various steps in the heme biosynthetic pathway (see Figure 13.1) with numerous mutations identified at each site.[29]

The porphyrias can be classified according to the main clinical features. Acute intermittent porphyria (AIP) and aminolevulinate dehydratase deficiency porphyria (plumboporphyria) are characterized by acute attacks that include neuropsychiatric manifestations. As photosensitivity and other cutaneous symptoms are the main clinical features of congenital erythropoietic porphyria, PCT, and erythropoietic protoporphyria, there are no special anesthetic or obstetric considerations for these three disorders other than meticulous skin care. However, PCT is associated with an increased incidence of diabetes, antinuclear antibodies, hepatitis B and C, HIV, and poor liver function.[31] Patients with hereditary coproporphyria (HC) and variegate porphyria (VP) have both acute attacks (see below) and skin manifestations.[32]

Epidemiology

Porphyrias are panethnic with an incidence between 0.5 and 10 per 100 000. Variegate porphyria is more common in the Africaaner community in South Africa with a frequency of up to 1 in 250.[33] Most of the porphyrias are inherited in an autosomal dominant manner with incomplete penetrance, although patients with aminolevulinate dehydratase deficiency porphyria are asymptomatic unless there is a homozygous defect.[29] The genetic mutations have been extensively studied and there appears to be many variants of each gene. Approximately 50% of patients who have the genetic defect actually manifest the

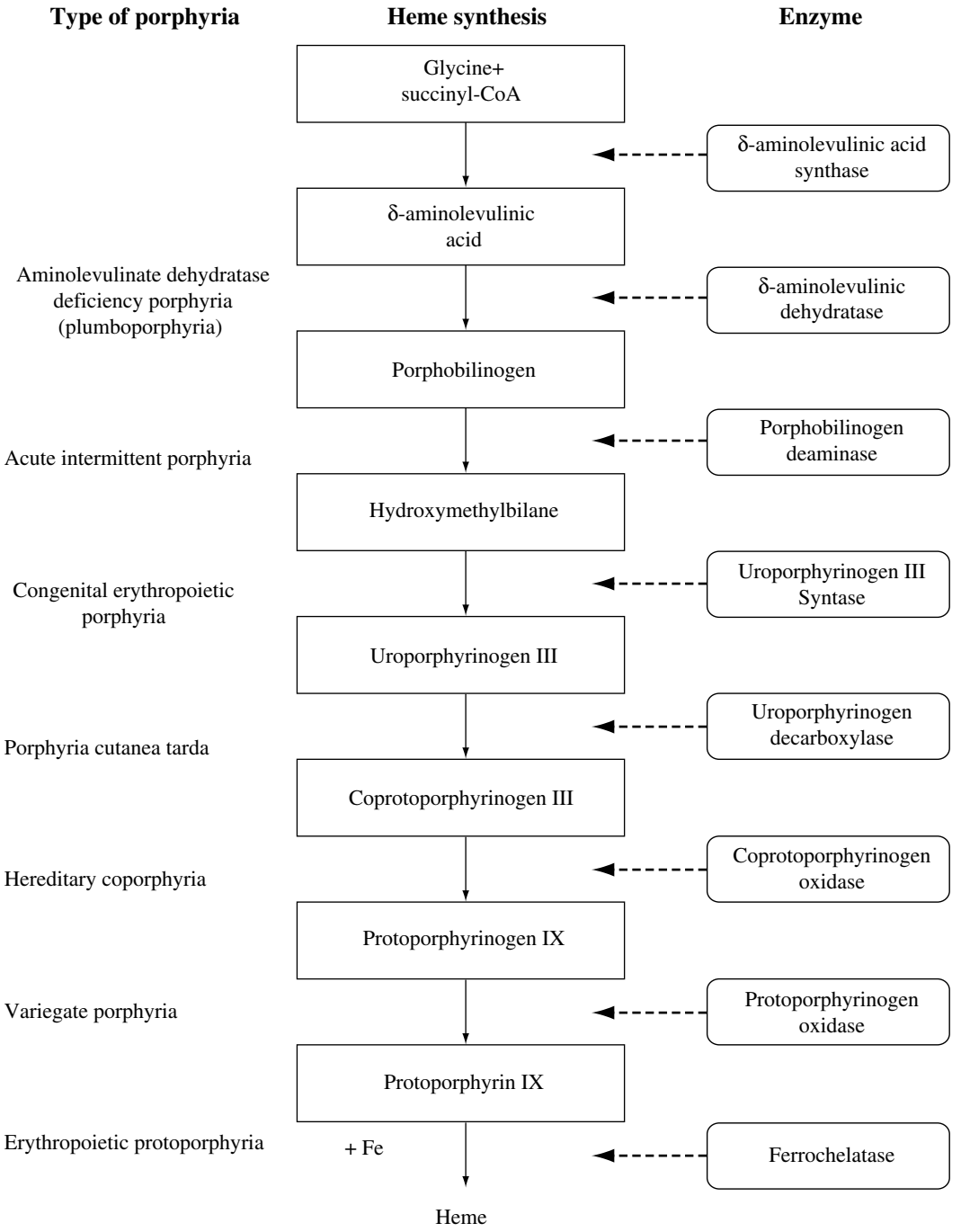

Figure 13.1 Enzyme defects at various stages in the heme biosynthesis pathway.

disease. Therefore, other factors such as modifying genes or environmental factors may play a crucial role in determining the phenotypic manifestations.[29] Acute intermittent porphyria occurs more commonly in women but VP is equally distributed between genders.[30]

Clinical manifestations of an acute attack

Acute attacks are often precipitated by factors that increase δ-aminolevulinic acid synthase activity resulting in increased production of porphyrinogens. These features include such factors as physiologic hormonal fluctuations, ethanol, fasting, dehydration, stress, and infection. Administration of enzyme-inducing drugs is the most important trigger factor under the direct control of the anesthesiologist (see Table 13.3).[33]

The pathogenesis of acute porphyria is unclear but probably involves direct neurotoxicity of δ-aminolevulinic acid, or porphobilinogen, or both. The liver seems to be an important source of these toxins since porphyrin metabolism returned to normal after liver transplantation in one symptomatic patient.[34] The clinical

Table 13.3 Examples of commonly used anesthetic and obstetric drugs and their recommended use in porphyria

Drug class	Agent	Recommendation
Inhalational agents	Nitrous oxide	Use
	Halothane	Use
	Enflurane	Probably safe
	Isoflurane	Probably safe
	Sevoflurane	Probably safe[a]
	Desflurane	Probably safe[a]
Intravenous induction agents	Propofol	Use
	Barbiturates	Avoid
	Ketamine	May not be safe[b]
	Etomidate	Avoid
	Alfaxalone/alfadolone	Avoid
Analgesics	Acetaminophen	Use
	Alfentanil/fentanyl/sufentanil	Use
	Remifentanil	Probably safe[a]
	Morphine	Use
	Meperidine	Use
	Nalbuphine	Probably safe[a]
	Naloxone	Use
	Ketorolac	No data
	Pentazocine	May be unsafe (animal data only)
Neuromuscular blocking agents	Tubocurare	Use
	Pancuronium	Use
	Succinylcholine	Use
	Vecuronium	Probably safe[a]
	Rocuronium	No data
	Mivacurium	No data
Neuromuscular block reversal agents	Atropine	Use
	Glycopyrrolate	Use
	Neostigmine	Use
Local anesthetics	Bupivacaine	Use
	Lidocaine	Use
	Prilocaine	Avoid[c]
	Procaine	Use
	Tetracaine	Use
	Ropivacaine	No data
	Cocaine	Avoid[c]
Sedatives and antiemetics	Droperidol	Use
	Domperidone	Use
	Phenothiazines	Use
	Lorazepam	Probably safe
	Diazepam	May be unsafe (animal data only)
	Oxazepam	May be unsafe (animal data only)
	Ranitidine	Use with caution
	Ondansetron	Use with caution
	Metoclopramide	Avoid
Obstetric medication	Oxytocin	Use
	Ergot derivatives	Avoid
	Misoprostil	Avoid
	Magnesium	Use
Cardiovascular drugs	Epinephrine	Use
	Alpha sympathomimetics	Use
	Beta sympathomimetics	Use
	Beta blocking agents	Use
	Calcium channel blocking agents	Use with caution
	Hydralazine	Avoid[c]
Miscellaneous	Phenytoin derivatives	Avoid
	Gabapentin	Use

[a] limited experience (at least one case report of successful use)
[b] at least one case of biochemical evidence of increased porphyrin production
[c] at least one acute attack thought to be precipitated (see www.emedicine.com/med/topic1880.htm)

manifestations of acute porphyria are a result of the effects of toxic metabolites (see Table 13.2). Many of the symptoms are non specific, leading to delays in diagnosis and treatment. The symptoms may vary in severity from mild to life-threatening. A family history of the disease is of prime importance in order to make the diagnosis. Acute attacks often begin with abdominal pain, autonomic instability, and electrolyte disturbances. Neuropsychiatric symptoms such as hallucinations and anxiety may also occur.

Neuromuscular weakness is potentially fatal and may lead to quadraparesis and severe respiratory failure. Sensory and motor neuropathies associated with porphyria are discussed further in Chapter 10. Seizures and cranial nerve palsies may result from central nervous system involvement.[35,36] Rarely, these defects can be permanent. In addition to neurotoxicity, porphyrin precursors may cause vascular damage leading to increased permeability of the blood–brain barrier resulting in focal brain edema and seizures.[29] Additional symptoms may be caused by the reduced heme in neural tissue. This reduction may lead to a lower concentration of heme-containing enzymes, resulting in deficiencies in neurotransmitters such as serotonin.[30] Various biochemical markers such as δ-aminolevulinic acid and porphobilinogen are diagnostic if found in the urine.

Obstetric implications

Because of hormonal changes, pregnancy may increase the incidence of acute attacks of porphyria. Many patients, previously asymptomatic, may have their first attack during pregnancy.[37,38] In a recent population-based study, 23% of patients with symptomatic AIP improved during pregnancy, 10% became worse, and 67% did not change.[39]

In a review published in 1977 by Brodie, 50 cases were evaluated.[40] The maternal mortality was 2% and fetal mortality 13%. Over 50% of affected women had an acute attack during pregnancy, 25% of these commencing after delivery, although many women were treated with unsafe drugs.[36] The risk of an attack appeared lower in VP (25%) and HC (33%).

A recent population-based study found that women with AIP who had repeated attacks of porphyria had a higher incidence of spontaneous abortion compared to those that did not. If no acute attacks occur, fetal outcome is good and pregnancy uneventful. Pregnancy does not appear to change the natural history of the disease.[39]

It may be difficult to distinguish an acute porphyric attack from eclampsia. Magnesium sulfate has been recommended as the tocolytic of choice in porphyria and is also the anticonvulsant of choice for eclampsia.[41]

Treatment of an acute attack

If the diagnosis of an acute attack of porphyria is likely (based on clinical and biochemical features) treatment should begin as soon as possible. Abdominal pain can be treated with opioids such as morphine since there is an extensive positive experience with this drug. Meperidine is also safe, but produces toxic metabolites if used in large doses. Intravenous fluids should be used to correct dehydration and electrolyte imbalance. Phenothiazines are safe and effective for nausea and vomiting. Beta-adrenergic blockers should be administered for symptomatic hypertension and tachycardia.[42] Several preparations of i.v. hemin are available and should be administered in doses of 3 to 4 mg/day. While heme arginate may be teratogenic, the drug is recommended for use later in pregnancy. Intravenous glucose may be used to resolve mild attacks or as a temporary measure until hemin is available.[42]

Anesthetic implications

Drug pharmacology

Great interest lies in drug-induced attacks, since many drugs that are commonly used during pregnancy and in anesthetic practice may be dangerous (see Table 13.3). The reader is referred to the excellent review by James and Hift[33] and the internet is another good resource for the most recent information.[43] The safety of drugs in porphyria is based on testing of in vitro chick embryos, standardized in vivo rat models, and clinical case reports. The evidence for many drugs is conflicting due to interspecies variations in response or because clinical experience is insufficient to draw firm conclusions. It is important to recognize precipitants other than drugs, and to be aware that known triggers do not consistently induce attacks. Hyperemesis gravidarum has been reported as a possible trigger.[39,44]

Regional anesthesia

While there is no evidence that regional anesthesia or analgesia may cause an acute attack of porphyria, there is reluctance to use it for fear of masking a potential peripheral neuropathy secondary to porphyria, or for medicolegal reasons.[45] While it is true that regional anesthesia may be excessively risky in an uncooperative patient, or in a patient who is hemodynamically unstable, local anesthetics such as lidocaine or bupivacaine, with or without fentanyl or sufentanil, are not porphyrogenic.[33] Both local anesthetics have been used frequently without triggering an attack. Epidural analgesia and anesthesia have been employed uneventfully in pregnant women with porphyria.[46,47,48,49] One could argue that an acute attack during labor could be prevented by using regional analgesia, as poor analgesia may cause fatigue, nausea, and vomiting – all recognized triggering factors. Whether or not regional analgesia is appropriate must be judged at the time of presentation. It is essential to see these women early in pregnancy to determine their baseline deficits (if any) and to formulate an analgesic plan. Parenteral opioids can be safely used in labor. The use of intramuscular meperidine and i.v. nalbuphine in combination with inhaled nitrous oxide/oxygen has recently been described in a symptomatic patient. She returned during a second pregnancy and received patient-controlled i.v. sufentanil.[45]

General anesthesia

No drugs, with the possible exception of sodium citrate, are known to be completely safe for prophylaxis against aspiration of gastric contents. Metoclopramide should be avoided.[49] Whether or not ranitidine is safe is controversial and so it should be used with caution.[33] After extensive experience, propofol appears to be the safest induction agent while thiopental and etomidate should be avoided. While there have not been any reported acute attacks caused by ketamine and it has been used safely, there has been a report of an increase in heme precursors in one patient.[50]

Rapid sequence induction and endotracheal intubation can be safely accomplished using propofol and succinylcholine. (Succinylcholine does not increase porphyrin production.) The use of rocuronium has not been reported. However, vecuronium has been used safely to maintain anesthesia in the parturient.[51] Atropine, glycopyrrolate, and neostigmine are safe. Halothane, isoflurane, and nitrous oxide can be used as inhalational agents.[33,43,51] There are recent reports of the successful use of sevoflurane[52] and desflurane[53] and they are likely to be safe, but there is far less clinical experience with these drugs in patients with porphyria. Postoperative analgesia may be accomplished using opioids and acetaminophen, but nonsteroidal anti-inflamatory agents such as diclofenac should be avoided.[33]

There are many drugs commonly used by obstetricians that should be avoided: including the ergot derivatives, calcium channel antagonists, hydralazine, clonidine, and α-methyl-dopa. Midazolam, temazepam, lorazepam, droperidol, and the phenothiazine antiemetics are likely safe. Oxytocin is not porphyrogenic and may be used. Severe post partum hemorrhage can be treated with carboprost (Hemabate®).[54]

Summary

Acute porphyrias are rare but may be triggered by both anesthetics and drugs commonly used in obstetrics. Further, labor

and delivery place the susceptible parturient at risk. While it is impossible to catalog or remember which drugs are safe, updated prescribing information is available on reliable websites. In spite of best efforts to reduce the risk in susceptible individuals, acute attacks may occur. The diagnosis must be considered and supportive treatment initiated early in parturients with a history of porphyria.

Increasing numbers of women with inherited metabolic disorders are surviving into adulthood and, with new therapies, are able to get pregnant and have successful outcomes. However, much experience is still being acquired in the management of inherited metabolic disorders during pregnancy. Some of these disorders can significantly affect the mother and the fetus. It is important to consider the possibility of an inherited metabolic disorder being present in fetuses of pregnancies affected by nonimmune hydrops, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome or acute fatty liver of pregnancy.[55] There is a need for ongoing collection of data within registries to improve our understanding of these conditions.[56]

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14 LIVER AND RENAL DISEASE

M. J. Paech and K. Scott

Liver disease

Effects of pregnancy on the liver

Pregnancy induces anatomic, physiologic, and functional changes in the liver because of an increase in serum estrogen and progesterone. These changes reverse postpartum, but can cause diagnostic difficulties during pregnancy if liver disease is present. For example, spider nevi and palmar erythema are stigmata of liver disease, but may be seen in some pregnant women in response to increased estrogen levels.

In normal pregnancy, liver size does not change significantly so hepatomegaly suggests liver disease. Hepatic blood flow remains unchanged, despite the physiologic increase in blood volume and cardiac output. In fact, the portion of cardiac output delivered to the liver falls by 35%. There is increased splanchnic, portal, and esophageal venous pressure in late pregnancy, and 60% of healthy women will develop esophageal varices that resolve postpartum. Clearance of drugs dependent on hepatic blood flow is reduced because of a larger volume of distribution.

Serum albumin concentration falls by up to 60% secondary to an increase in plasma volume, leading to a fall of total serum protein by 20% in mid-pregnancy. Serum globulins alter slightly, with an increase in α and β fractions, and α-fetoprotein concentration, but a reduction in γ-globulin. There is increased production of fibrinogen and factors VII, VIII, IX, X and von Willebrand factor. Ceruloplasmin and transferrin levels increase, as do several specific binding proteins (e.g. thyroxine, vitamin D, and corticosteroids). There are minor changes in porphyrin metabolism. Serum bilirubin tends to fall because of hemodilution and a lower albumin concentration, so an increase in serum bilirubin suggests liver disease.

Serum triglycerides rise progressively to term, as do very-low density lipoproteins and serum cholesterol. Serum alkaline phosphatase (ALP) increases four-fold by the third trimester and returns to normal by three weeks postpartum. Serum lactate dehydrogenase (LDH) is normal or marginally increased, whereas serum γ-glutamyl-transpeptidase (GGT) declines slightly and 5′ nucleotidase increases slightly. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) remain within the normal range (see Table 14.1).[1,2]

Causes of liver disease in pregnancy

Various congenital and acquired liver diseases may present during pregnancy (see Tables 14.2 and 14.3). The most common is viral hepatitis, but a number of uncommon diseases unique to pregnancy are important causes of mortality. Women with cirrhosis, portal hypertension, acute liver failure, or hepatic rupture pose major anesthetic challenges, while many uncommon conditions involving the liver confer minimal or no risk to mother or fetus. These relatively benign disorders include the hyperbilirubinemias, which are characterized by elevations of unconjugated bilirubin (Gilbert disease) or conjugated bilirubin (Dubin-Johnson and Rotor syndromes). Bilirubin concentrations rise during pregnancy in about 50% of women affected by these disorders, but fetal outcomes are good. Several multisystem diseases involve the liver, including preeclampsia, systemic lupus erythematosus, and hemachromatosis.

Viral hepatitis

Viral hepatitis (see Table 14.4) is the most common cause of hepatic dysfunction and jaundice in pregnancy.[1,2,3,4,5,6,7] In addition to hepatitis A, B, C, D, E, and G viruses, a number of other viruses cause hepatitis during the acute systemic infection phase, especially in immunosuppressed patients. These other viruses include herpes simplex virus (HSV), which is more likely to cause fulminant hepatitis in the pregnant patient than in the nonpregnant patient, cytomegalovirus, and Epstein Barr virus. Herpes simplex virus hepatitis causes a prodromal illness with fever, oropharyngeal or genital lesions, coagulopathy, and very high serum aminotransferase, but near normal bilirubin levels. Treatment with acyclovir is appropriate and results are encouraging.[6] Health care workers are at risk of contracting hepatitis, especially hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV), through blood contact, so the application of universal precautions is essential.

Hepatitis A

Hepatitis A virus (HAV) infection varies in prevalence geographically and is endemic in Africa, Asia, and Central America. Transmission is fecal–oral and most infections are asymptomatic or subclinical, but serum AST and ALT levels are elevated. Immunoglobin M anti-HAV is present in acute infection and since HAV clears after a few weeks, acquired immunity (anti HAV IgG-positive serostatus) is achieved.

Hepatitis A virus affects 1 in 1000 pregnant women in the USA. The clinical presentation in pregnancy differs in that pruritus is more common, because of high estrogen levels. Treatment is supportive. Both inactivated vaccine and postexposure immunoglobulin prophylaxis are safe during pregnancy. Although vertical transmission has not been described, immunoglobulin may be given to the neonate and close household contacts, and breastfeeding should be encouraged.[3,4,5,6,7]

Obstetric Anesthesia and Uncommon Disorders, eds. David R. Gambling, M. Joanne Douglas and Robert S. F. McKay. Published by Cambridge University Press.

Table 14.1 Liver function tests in normal pregnancy

Test	Pregnancy effect	Trimester of maximum change
albumin	↓ 20–60%	2
α-globulin	slight ↑	3
β-globulin	slight ↑	3
γ-globulin	nil to slight ↓	3
fibrinogen	↓ 50%	2
ceruloplasmin	↑	3
transferrin	↑	3
bilirubin	nil	–
alkaline phosphatase (ALP)	2–4 × ↑	3
γ-glutamyl-transpeptidase	nil or slight ↓	–
lactate dehydrogenase	nil or slight ↑	3
aspartate aminotransferase (AST)	nil	–
alanine aminotransferase (ALT)	nil	–
5′ nucleotidase	nil or slight ↑	–
bile acids	nil	–
triglyceride	2–3 × ↑	3
cholesterol	2 × ↑	3

Hepatitis B

Hepatitis B virus is a highly infectious double-stranded enveloped virus transmitted by cutaneous (especially needle sharing) or mucosal exposure, sexually, and vertically from mother to fetus. Most acute infections are subclinical, but nausea, vomiting, abdominal pain, and jaundice may occur. During the acute phase, the diagnosis is made by detection of HBV surface antigen in the serum or other secretions and is confirmed by detection of IgM antibodies to HBV core antigen. Hepatitis e (envelope) antigen is also present and as anti-HBVe antibody develops, patient infectivity decreases, but infectivity remains when HbsAg is present. About 5% of patients develop chronic infection.

Acute HBV complicates 1 in 500–1000 pregnancies in the USA, and chronic HBV infection is present in up to 1.5% of pregnant women. The presence of HbsAg does not pose additional risk for the pregnancy. Interferon, used for those with active disease and liver damage, has many side effects and patients taking interferon should not become pregnant. Transplacental transmission of HBV occurs in early pregnancy occasionally, but most perinatal transmission takes place intrapartum. The risk of mother-to-child transmission increases as pregnancy advances, increasing from 10% in the second trimester to 90% in the third trimester in HBVeAg positive women. Passive and active immunization is highly effective in preventing neonatal transmission, and children born to mothers at high risk can be vaccinated.

Hepatitis C

Hepatitis C is the most common chronic bloodborne infection in the USA accounting for 20% of acute viral hepatitis.[7] Hepatitis C virus produces a six- to nine-week illness that is often subclinical or mild. Chronic infection is common and long-term sequelae include cirrhosis, liver failure, and hepatocellular carcinoma. The prevalence of HCV varies geographically from 1 to 6%, and areas with high endemic rates include Asia, Middle East, Africa, and southern and eastern Europe. Hepatitis C virus infection is increasing in other countries, often from intravenous drug use (IVDU), blood transfusion, incarceration, tattooing, body piercing, and organ transplantation. Chronic hepatitis develops in 70% of infected individuals, most of whom remain asymptomatic. Of those, 20% will develop cirrhosis within 40 years of viral acquisition and a small number will develop hepatocarcinoma.[4,5,6,7]

The risk of sexual transmission is low, but vertical transmission from mother to fetus occurs in 6% of women who are HCV polymerase chain reaction (PCR) positive. Quantitative HCV-RNA testing is a marker of the risk of vertical transmission, and more often positive in the presence of coinfection with human immunodeficiency virus (HIV) and certain HCV genotypes.[5,7] As with HIV, transmission occurs mainly at delivery, through contact with contaminated vaginal secretions. There is no association between vertical transmission of HCV and gestational age at delivery or the presence of chorioamnionitis.[7] Elective cesarean section (C/S) is not necessary to reduce viral transmission in HCV infected women. However, HCV/HIV-coinfected women may require C/S based on HIV status (see Chapter 18). Both HBV and HCV are detectable in human milk but breast-feeding is considered safe as long as there is no coinfection with HIV.[7] Surveillance of the neonate is by HCV antibody screen at 12 months (maternal antibody detectable for 18 months) or HCV-RNA by PCR within the first few months of life. There is no vaccine or immunoglobulin to prevent spread of the disease.

During pregnancy, liver function tests often return to normal. The treatment of HCV includes drugs such as interferon and ribavirin, although in most cases these fail to clear the infection. These drugs are only appropriate after pregnancy because they are teratogenic and have serious adverse effects.

Hepatitis D, E, and G

Hepatitis D virus is a single-stranded RNA virus that depends on the presence of HBV for replication. Infection is more common in IVDU and is endemic in some areas, e.g. southern Italy.[6] Coinfection with HDV and HBV is associated with more severe disease and a higher chronicity rate than HBV infection alone. Up to 80% of coinfected patients develop cirrhosis more rapidly than seen with HBV infection alone. Infection is rare in pregnant women and children, which suggests vertical transmission is uncommon.

Hepatitis E virus (HEV) is a single-stranded, nonenveloped RNA virus, endemic in some parts of Africa, India, and Mexico. It shares similarities with HAV and is spread via the fecal–oral route. Acute infection in pregnancy, especially the third trimester, can cause fulminant hepatitis with 20% mortality. Vertical intrapartum transmission occurs in 50–100%, conferring a high risk of neonatal hepatic failure.[5,6,7]

Hepatitis G virus (HGV) can only be detected by reverse-transcriptase PCR and the epidemiology parallels that of HIV and other hepatitis viruses. Transmission is similar to HCV, but significant liver disease is unlikely. Vertical transmission occurs in 60% of cases, without detriment to the infant.[6]

Table 14.2 Liver diseases unique to pregnancy (excluding preeclampsia)

Disorder	Key clinical features	Obstetric implications	Anesthetic implications
Acute fatty liver of pregnancy (AFLP)	1. Third trimester malaise, nausea, abdominal pain, and, later, jaundice. 2. Hypoglycemia, metabolic acidosis, coagulopathy, liver and hepatorenal failure. 3. Preeclampsia in 40%. 4. Intensive supportive care including dextrose, antibiotics, vitamin K. Expedite delivery. 5. Complete postpartum resolution.	1. Intensive fetal monitoring. 2. Early delivery mandatory.	1. Optimal medical management; invasive monitoring. 2. Plan for C/S. 3. Correct coagulopathy and use regional if not contraindicated. 4. Prepare for peripartum or postpartum hemorrhage. 5. Use anesthetic and analgesic drugs appropriate to severe hepatic dysfunction.
Intrahepatic cholestasis of pregnancy (IHCP)	1. Late pregnancy pruritus, then malaise and mild jaundice. 2. Treat pruritus with ursodeoxycholic acid. 3. Rapid postpartum resolution.	1. Monitor fetal status. 2. Preterm delivery, C/S and poor fetal outcome common.	1. Monitor liver function and coagulation. 2. Prepare for C/S, postpartum hemorrhage.
Hyperemesis gravidarum	1. Severe vomiting and dehydration in early pregnancy. 2. Minor liver function abnormalities. 3. Occasionally severe complications as a result of vomiting.	1. Increased risk of early fetal loss but otherwise good outcomes.	1. Optimal antiemetic therapy. 2. Correct fluid and electrolyte imbalance.

Table 14.3 Rare liver diseases

Disorder	Key clinical features	Obstetric implications	Anesthetic implications
Wilson disease	1. Excessive copper deposition in liver and brain, causing hepatic dysfunction and motor or psychiatric disturbance. 2. Chelators or binding agents to reduce copper levels. Zinc recommended.	1. Subfertile unless well controlled. 2. Continued treatment to avoid relapse.	1. Monitor liver function; coagulation; esophageal varices; bulbar involvement; and drug effects. 2. Use anesthetic drugs appropriate for patients with severe liver dysfunction. 3. Prepare for postpartum hemorrhage.
Budd-Chiari syndrome	1. Hepatic vein obstruction causing ascites, hepatomegaly, and liver failure. 2. Coagulopathy common. 3. May be associated with prothrombotic and other disorders.	1. Consult a hepatic physician. 2. Anticoagulation and portocaval shunt may be required. 3. Poor maternal and fetal prognosis.	1. Monitor liver function, coagulation. 2. Use anesthetic drugs appropriate for patients with severe liver dysfunction.
Primary biliary cirrhosis	1. Variable presentation from asymptomatic to cirrhosis. 2. Diagnosis based on mitochondrial antibodies and liver biopsy.	1. Pregnancy and the fetus unaffected if well-compensated disease.	1. Monitor liver function and coagulation. 2. Use regional block if possible and anesthetic drugs appropriate to severe liver dysfunction.

Anesthetic implications of viral hepatitis

The onset of inflammatory hepatocytic disease can be gradual or sudden with incubation periods from 2–24 weeks. Clinically the patient may be anorexic, jaundiced, fatigued, and will demonstrate dark urine in most cases. In addition, the patient may have nausea, fever, and abdominal pain. There may be mild anemia, vitamin K deficiency, lymphocytosis, and coagulation abnormalities. Fulminant hepatic failure is uncommon (the incidence is the

Table 14.4 Acute viral hepatitis in pregnancy

Risk factors	Physical features	Laboratory tests
Intravenous drug use	No findings of chronic liver disease	Blood picture
Sexual contact	Tender hepatomegaly	Coagulation tests
Contact with infected persons	Jaundice	s. albumin, s. bilirubin
Travel to countries where hepatitis is endemic	Skin lesions with HBV & HSV	s. ALP
Body piercing	Subclinical (HCV)	s. ALT/AST
Blood transfusion (extremely rare)		HAV IgM
Drug-induced hepatitis mimics		HBVsAg
		HBVeAg
		HBVcAb
		HCVAb
		HEV Ab
		HSV IgM
		CMV IgM
		EBV IgM

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; CMV = cytomegalovirus; EBV = Epstein Barr virus; sAg = surface antigen; eAg = envelope antigen; cAb = core antibody; Ab = antibody; IgM = immunoglobulin M; s. = serum

same in pregnant and nonpregnant women), occurs more in late pregnancy and with HEV infection, and is associated with a poor prognosis. The incidence of preterm labor, fetal demise, and neonatal asphyxia is higher in patients with fulminant hepatitis. Hepatic encephalopathy and hepatorenal syndrome have a higher incidence during pregnancy.

In the absence of advanced disease, infectious complications during pregnancy are often minor.

If anesthesia is required it is important to remember that halothane and sevoflurane have been associated with fulminant liver failure[8] and severe acute hepatitis.[9] Ketamine may have hepatoprotective effects mediated through a reduction in cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) protein. In the absence of shock or coagulopathy, regional anesthetic techniques are suitable; however, it has been shown that general anesthesia does not affect survival in patients with advanced liver disease.[10]

Hyperemesis gravidarum

Most women experience nausea and vomiting in early pregnancy, which usually resolves by 12–16 weeks' gestation. Hyperemesis gravidarum (HG) is protracted nausea and vomiting of sufficient severity that adequate hydration and nutrition are not maintained. Risk factors include nulliparity, younger age, high saturated fat intake and obesity, female fetus, twins, and hydatidiform mole. The incidence is 0.5–10 per 1000 pregnancies and the condition may recur in a subsequent pregnancy. Fetal outcome is usually good, although in more severe cases birthweight is reduced. Fetal death is common if the mother develops Wernicke encephalopathy.[11]

Vomiting may lead to dehydration, ketosis, weight loss, and reflux esophagitis. Biochemical abnormalities include hypochloremic alkalosis, electrolyte disturbance (severe hyponatremia and hypokalemia) and mild hyperthyroidism (from elevated human chorionic gonadotrophin [HCG]). Abnormal liver function, usually consisting of mild serum transaminases elevation, occurs in almost 50% of women with HG. The etiology and mechanism of liver disease in HG is uncertain, but it may be related to impaired fatty acid oxidation.[12] Synthetic liver function remains normal and abnormalities reverse with treatment.

Hyperemesis often leads to hospitalization (and sometimes multiple admissions) and may cause a psychological disturbance. Rarely, repeated vomiting leads to esophageal rupture, pneumomediastinum, renal failure, or death from aspiration or Wernicke encephalopathy from thiamine deficiency.[13,14]

Management

Hospitalization is necessary for intravenous fluid replacement, monitoring, antiemetic therapy, psychological therapy, and, occasionally, parenteral or enteral nutrition. Fluid and electrolyte abnormalities must be corrected. Hyponatremia is common and sodium-containing crystalloid fluids, with or without potassium, should be given cautiously, avoiding rapid correction and the risk of central pontine myelinosis. Intravenous dextrose and carbohydrate loading should be avoided and thiamine and other vitamin deficiencies, especially of the B group, corrected. Safe antiemetic drugs include metoclopramide, droperidol, antihistamines, and 5-hydroxytryptamine-3 receptor antagonists. Histamine receptor blockers or proton pump inhibitors may be useful in preventing esophagitis. Iatrogenic complications result from central venous catheterization, parenteral nutrition, or drug side-effects.[14]

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (IHCP) (see Table 14.5) is the second most frequent cause of cholestasis and jaundice during pregnancy, after viral hepatitis. The prevalence is <1 in 1000 (0.1%), but in Scandinavia and Chile it reaches 2–25% in certain populations. Many cases are subclinical[1] and recurrence in subsequent pregnancies is common. Intrahepatic cholestasis of pregnancy is a genetic disorder predisposing a woman to increased cholestasis during pregnancy or while taking oral contraceptives.[15] Among women who develop jaundice on oral contraceptives 50% have had IHCP in a prior pregnancy, and IHCP is more common with advanced maternal age and multiparity.[1,4] Most cases occur in the second half of pregnancy, although IHCP can occur as early as 6 weeks.[4] Intrahepatic cholestasis may be due to dysfunction of bile secretion by active hepatocellular transporters,[16] resulting in intracellular accumulation of toxic bile acids causing liver cell injury. Liver biopsy shows dilated bile canaliculi, minimal inflammatory response, and nonspecific cholestasis.[17]

Table 14.5 Intrahepatic cholestasis of pregnancy (IHCP)

Clinical features		
	onset third trimester, sometimes second	
	pruritus prominent	
	jaundice mild	
	no anorexia, malaise, or fatigue	
	genetic disposition	
	recurrence common	
Laboratory changes		
	s. bile acids	10–100 fold increase
	s. ALP	7–10 fold increase
	s. ALT/AST	2–10 fold increases
	s. GGT	normal
	s. bilirubin	normal or slight increase
	s. cholesterol	2–4 fold increase
	s. triglycerides	normal to slight increase
	prothrombin time	normal to 2 fold increase
Differential diagnosis		
	viral hepatitis	
	cholelithiasis	
	autoimmune disorders	
	sclerosing cholangitis	
	primary biliary cirrhosis	
	extrahepatic cholestasis	
	drug toxicity	
	Dubin-Johnson syndrome	

ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ-glutamyl-transpeptidase; s. = serum

Common symptoms include malaise, abdominal discomfort, subclinical steatorrhea, and pruritus. Abdominal pain warrants investigation for viral hepatitis or cholelithiasis (see Table 14.5). Pruritus results from reduction in bile flow, and reduced bile and bile salt excretion, and typically starts in the extremities (palms and soles) before extending to the trunk and face. Although elevation of plasma bile salts is associated with itching, there is no correlation between the concentration of bile salts and severity of the itch. Itching is often severe, disrupts sleep at night, responds poorly to treatment and, after one to two weeks, mild jaundice appears in 50% of cases. Other causes of pruritus should be ruled out, including thyroid disease, renal failure, lymphoma, anemia, and drug reactions. Physical examination is usually normal in IHCP, but skin excoriation from scratching may be seen. The earliest biochemical changes are a 10–100 times increase in serum bile acids. The measurement of glutathione S-transferase alpha (GSTA), a specific marker of hepatocellular integrity, distinguishes women with IHCP from those with benign pruritus gravidarum.[18] Serum bilirubin is typically elevated. Although transaminases may increase as much as two- to ten-fold (up to 1000 U/l) in 60% of cases, moderate to severe elevations suggest the possibility of other hepatic disease such as drug-induced or viral hepatitis. Gamma-GT is usually normal.

Obstetric implications

Intrahepatic cholestasis of pregnancy poses few maternal problems, but there is poor fetal prognosis from transfer of bile acids from mother to fetus (bilirubin does not cross the placenta significantly). Accumulation of bile acids in the cord blood serum, meconium, and amniotic fluid may account for diminished fetal well-being and sudden intrauterine death in IHCP. More severe cases are associated with low birth weight and prematurity,[19] but perinatal mortality does not differ from that of the general population. In women with IHCP, ursodeoxycholic acid (UDCA) therapy and close maternal–fetal surveillance is indicated. Delivery should occur near term following confirmation of fetal lung maturity, or earlier if the fetus is compromised. Ursodeoxycholic acid is a hydrophilic bile acid that displaces toxic bile acids from hepatic membranes, reducing the toxic bile acid content in both mother and fetus.[20] Ursodeoxycholic acid also lowers the amount of bile acids present in colostrum. Ursodeoxycholic acid is safe and more effective than cholestyramine and has replaced it in the treatment of IHCP.[20] Ursodeoxycholic acid is especially useful in severe forms of IHCP, or when there is a history of sudden fetal death in a previous pregnancy.[21] In one series,[22] twelve pregnancies were managed expectantly and there were eight stillbirths and two premature deliveries (fetal distress with one death, one C/S for fetal distress). Subsequently, these investigators treated three women who had IHCP with UDCA. No perinatal morbidity or mortality occurred. Intrahepatic cholestasis of pregnancy starts to resolve spontaneously within 24 hours of delivery, although jaundice and abnormal liver function tests may persist for months. If symptoms of liver disease persist beyond this time then chronic hepatopathy must be ruled out.

Management and anesthetic implications

Concerns for the anesthesiologist in IHCP include the degree of hepatic disease and the possibility of planned near-term obstetric interventions (e.g. early induction of labor). Decreased small intestinal bile acid concentrations can lead to impaired absorption of fats and fat-soluble vitamins, resulting in steatorrhea and deficiencies in vitamins A, D, E, and K.[23] Although unusual, coagulopathy may occur with IHCP and a case of epidural hematoma complicating cholestasis of pregnancy has been reported.[24] Injection of vitamin K and fresh frozen plasma can prevent coagulopathy. If cholestyramine is used, prophylactic vitamin K should be given. There is an increased risk of postpartum hemorrhage (PPH) so the patient should have blood crossmatched and large-bore intravenous lines inserted.

Ondansetron may be effective treatment for IHCP-associated pruritus.[25] Opioids, especially neuraxial opioids, may exacerbate the pruritus, but effective pain management should be used.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare and potentially fatal disorder with an incidence of 1 in 7–15 000 pregnancies.[26,27] It presents in the third trimester, often close to term, although it can occur earlier.[28] Acute fatty liver of pregnancy affects all ages, races, and ethnicities, and may appear after several normal pregnancies.

Acute fatty liver of pregnancy is most common in twin, nulliparous, and male-fetus pregnancies[29] and recurrence in a subsequent pregnancy is unusual.[30] Early diagnosis may be difficult, since 40% of cases have preeclampsia, and 20% have hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.[30,31] Greater awareness, intensive therapy, and prompt delivery of the fetus have resulted in a significant reduction in maternal mortality.[27,32]

Metabolic, synthetic, and excretory functions of the liver are abnormal due to fat infiltration and inflammation.[1,2,3,4,5,6,30] Acute fatty liver of pregnancy occurs in 30–80% of pregnancies in which the fetus has a long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. Long-chain 3-hydroxacyl-CoA dehydrogenase is one of four enzymes that are part of a trifunctional protein complex on the inner mitochondrial membrane, responsible for long-chain fatty acid metabolism in the liver. When the infant of a heterozygous woman is homozygous or even heterozygous for one of these mutations, it is unable to oxidize 3-hydroxy fatty acids, and may present in infancy or after extended fasting with a Reye-like syndrome.[1,2,3,4,6,33] During pregnancy, excess fetal fatty acids transfer to the mother and accumulate in her liver. Acute fatty liver of pregnancy may also be associated with deficiencies in carnitine palmitoyltransferase I, and medium- and short-chain acyl-CoA dehydrogenase.[34] Serum bilirubin and aminotransferases are usually moderately elevated and serum AST levels are ~300U/l (up to 1000U/l). Hypoglycemia can result from depression of glucose-6-phosphatase activity and is often profound. Marked neutrophil leukocytosis to 30 000/mm^3, with left shift, and microangiopathic hemolytic anemia with thrombocytopenia are frequently present. Disseminated intravascular coagulation with elevated fibrin degradation products and low fibrinogen are less common. Oliguria may be accompanied by abnormalities of serum electrolytes and of urine biochemistry. Elevated serum creatinine and ammonia levels occur, even in early disease, and metabolic acidosis results from high serum lactate levels.[1,2,3,4,6,30]

Table 14.6 Acute fatty liver of pregnancy (AFLP)

Clinical features		
	Onset second half of pregnancy	
	Nausea, vomiting, malaise, and jaundice prominent	
	Hypoglycemia prominent	
	Preeclampsia often coexists (features are hypertension, proteinuria, right upper-quadrant pain)	
	Abdominal pain	
Less common presentations		
	Headache	
	Backache	
	Hematemesis	
	Necrotizing enterocolitis	
	Fulminant acute liver failure (severe hypoglycemia, renal failure, lactic acidosis, gastrointestinal bleeding, and impaired consciousness or encephalopathy)	
Laboratory changes		
	s. bilirubin	normal or slight increase
	s. ALT/AST	increase to 1000 U/l
	s. GGT	slight increase
	s. fibrinogen	low
	prothrombin time	high
	blood glucose	low
	s. uric acid	increased
	s. ammonia	increased
	platelet count	normal or low

AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ-glutamyl-transpeptidase; s. = serum

Clinical features

The symptoms of AFLP develop over one to seven days and include malaise, nausea and vomiting, abdominal pain, fever, and jaundice, although there are a variety of less frequent features (see Table 14.6). Jaundice is more common with viral hepatitis, cholestasis, bile duct obstruction, or preeclampsia. Pruritus is uncommon (incidence 5–30%), tachycardia is common, and the liver size is normal.[1,2,3,4,5,30] Other complications include renal failure, acute respiratory distress, and diabetes insipidus. Pancreatitis, with pseudocyst formation and retroperitoneal bleeding, may occur in those with severe disease and is detected by imaging studies, and an elevated serum lipase, or, less frequently, amylase.[35]

Although AFLP can be confused with severe preeclampsia, distinguishing features are hypoglycemia, hyperammonemia, and less chance of right upper quadrant (RUQ) pain or hypertension. The diagnosis is based on typical clinical and biochemical findings (mildly elevated aminotransferases between 100 and 1000 U/l, mildly elevated bilirubin, and increased ammonia). Other differential diagnoses include cholestasis and viral hepatitis. Ultrasonographic or computed tomographic (CT) imaging to detect liver fat accumulation is not always positive, but may reveal other liver or biliary tract abnormalities. Diagnostic liver biopsy is often precluded by the bleeding risk.[1,2,3,4,5,30]

Management and obstetric implications

Appropriate supportive therapy is based on invasive monitoring, and correction of hypoglycemia and coagulopathy. About 50% of cases have coagulopathic bleeding, requiring transfusion of blood products; this may worsen postpartum when antithrombin levels fall further.[30] Gastrointestinal hemorrhage, sepsis, pancreatitis, or diabetes insipidus may also require treatment. In those with preeclampsia, adjustment of the dose of magnesium is necessary when renal impairment is present. Patients who develop encephalopathy may require intubation and ventilation.

After resuscitation and stabilization, expeditious delivery is essential and improvement in liver function invariably follows, which improves maternal prognosis.[27,31] Fetal and neonatal abnormalities include prematurity, intrauterine growth restriction, intrapartum hypoxia, and hypoglycemia. Neonates with LCHAD deficiency can experience failure to thrive, hepatic failure, cardiomyopathy, hypoglycemia, and death.[32,33] In the postpartum period maternal recovery is rapid, starting with normalization of prothrombin time followed by a return to normal of all liver function tests within four weeks. Nevertheless, intensive care is still required for several days

postpartum because of the risk of maternal hypoglycemia. Genetic counseling should be offered about future risk of recurrence.

Anesthetic implications

The anesthesiologist should assist with optimization of medical therapy by initiating invasive monitoring. Blood pressure (BP), blood glucose, fluid balance, electrolytes, coagulation, and acid–base status need regular assessment. Arterial cannulation is valuable and good venous access via a central venous or peripherally inserted central catheter assists with infusion of dextrose and parenteral nutrition, correction of low serum calcium and hypovolemia, maintenance of adequate urinary output, and treatment of hypertension. Prophylactic administration of an H_2-receptor antagonist is warranted to reduce the risk of gastric erosion, ulceration, and esophagitis. Coagulopathy is common so administer vitamin K with blood products reserved for a bleeding diathesis. Successful liver transplant has been reported,[36,37] the primary indications being raised intracranial pressure or deterioration of neurologic function.

There are few reports describing the anesthetic management of patients with AFLP. Uneventful epidural anesthesia, which preserves hepatic blood flow, has been described;[38] however, in all but mild cases, coagulopathy contraindicates regional anesthesia. Consequently, general anesthesia usually is required for C/S.[39,40,41] In such cases, or if severe thrombocytopenia is present, intramuscular injections, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided. If regional block is suitable, an argument can be made for spinal anesthesia, because of the smaller needle and lower risk of vascular bleeding. If epidural anesthesia is used it is advisable to remove the epidural catheter immediately after delivery.

Aims of general anesthesia are to maintain liver and renal blood flow and avoid hepatotoxicity. As propofol has normal pharmacokinetics in cirrhosis and does not alter hepatic blood flow it may be the best induction agent.[42,43] Desflurane has negligible hepatic metabolism[44] while prolonged administration of isoflurane causes mild derangement of hepatocellular function in healthy individuals.[44] Nitrous oxide should be avoided. Succinylcholine is not contraindicated, but may cause prolonged neuromuscular block due to a low plasma cholinesterase. Atracurium is the preferred nondepolarizing neuromuscular blocking drug. Rocuronium shows great individual variability among patients with hepatic impairment.[45] In the presence of fulminant hepatic failure, exaggerated responses to anesthetics and opioid analgesics may occur because of poor metabolism and central depression associated with encephalopathy.

Cirrhosis and portal hypertension

Cirrhosis is caused by a number of conditions, especially chronic hepatitis C, D, and E, or alcoholism, but is rare in women of childbearing age (incidence 1 in 2000).[46] Pregnancy is less common in advanced cirrhosis as altered metabolism of the sex steroids leads to infertility, but improvements in care mean that women with well-compensated cirrhosis may become pregnant. In approximately 25% of pregnant women with cirrhosis, liver function will deteriorate[47] and portal venous pressure will increase resulting in esophageal varices, ascites, and portal hypertensive encephalopathy.

Portal hypertension may occur in the absence of cirrhosis from portal vein thrombosis or congenital hepatic fibrosis. In pregnancy, the diversion of blood through the azygous venous system and reflux esophagitis further predispose to variceal bleeding. Sixty percent of women with varices suffer hematemesis, especially during late pregnancy[47,48] and this is associated with a 30% mortality rate.[46,47] Therapy includes beta-blockade to lower portal pressure, sclerotherapy, and banding, but if these fail surgical intervention such as spleno-renal shunt may be required.[49] Women with existing shunts are at a lower risk of hematemesis and the outcome of pregnancy is usually good.[1] Fifty percent of patients with cirrhosis and significant portal hypertension develop a complication such as anemia from chronic illness or bleeding varices, and thrombocytopenia as a result of hypersplenism. Rupture of a splenic artery aneurysm occurs in approximately 2% and is associated with very high maternal and fetal mortality.[3]

Obstetric and anesthetic implications

Deterioration of hepatic function during pregnancy is precipitated by bleeding, sepsis, hypotension, or drugs, including analgesics. Drugs with antiplatelet activity potentiate the bleeding risk. Impaired acetaminophen and morphine-3 and 6-glucuronide metabolism may produce hepatic toxicity and central nervous system depression respectively, so opioids without active metabolites, such as fentanyl, are preferable. Intra-abdominal surgery on patients with advanced cirrhosis is associated with high 30-day mortality (60% or more), especially if emergency surgery is required or the patient is significantly coagulopathic.[50] Spontaneous abortion and neonatal mortality rates are increased.[47,51]

The presence of midline varices and caput medusa may favor a vaginal delivery rather than C/S.[52] If vaginal delivery is planned and coagulation is normal, epidural or spinal analgesia will prevent straining during delivery.[53] If general anesthesia is required, the principles of anesthesia that pertain to acute liver failure (see below) are applicable.

Liver tumors

Pregnancy complicated by hepatocellular carcinoma, cholangiocarcinoma, hepatic adenoma, and focal nodular hyperplasia (a vascular benign tumor) is very rare. Hepatocellular carcinoma is a very rare primary malignancy or more often, secondary to chronic hepatitis, especially HCV hepatitis. Benign hepatic adenomas occur almost only in women, and oral contraceptives are implicated in the pathogenesis. During pregnancy, estrogens may stimulate tumor growth, and hemorrhagic rupture into the tumor or abdominal cavity occurs in 25% of cases. This event is associated with high maternal and fetal mortality.[54,55] Termination of pregnancy is recommended, but successful resection of adenomas > 5 cm, or of carcinoma by partial hepatectomy in the second trimester has been performed.[56,57] Presence of cirrhosis and metastatic disease requires assessment and careful preoperative planning. Intraoperative fetal monitoring is warranted if the fetus is viable. If resection is attempted, massive hemorrhage is expected and cell salvage should be considered.

Table 14.7 Features of hepatolenticular degeneration (Wilson disease)

Usually asymptomatic until early adulthood

50% present with hepatic involvement
- acute and chronic hepatitis
- cirrhosis
- fulminant hepatitis with hemolytic anemia

50% present with neurologic, psychiatric, or behavioral abnormalities
- loss of fine hand movements
- tremor
- loss of coordination
- chorea
- dysphagia
- dysarthria

Hepatolenticular degeneration (Wilson disease)

Hepatolenticular degeneration or Wilson disease is an autosomal recessive disorder, involving a gene on chromosome 13 that encodes a copper-transporting ATPase. More than 20 gene mutations account for variable clinical expression, resulting in reduced copper excretion into bile, and inhibition of the plasma copper binding transport protein ceruloplasmin.[2,54] The worldwide prevalence is 1 in 20 000.[58] Copper is an inorganic nutrient, essential to life, and is present in cytochrome C oxidase, monoamine oxidase, and tyrosinase. The accumulation of free and tissue copper damages the liver, brain, and other organs, although not usually the kidney.

The diagnostic features of Wilson disease are liver disease and movement abnormalities (Table 14.7), although occasionally repeated spontaneous abortion or amenorrhea, or the presence of golden deposits of copper in Descemet's membrane of the cornea (Kaiser-Fleischer rings) leads to the diagnosis. The diagnosis is by low plasma and high urinary copper levels and very low plasma ceruloplasmin, or by liver biopsy with copper assay.[2,3,54]

Treatment and obstetric implications

Treatment consists of eliminating foods containing copper, and removing and detoxifying copper deposits. If untreated the disease is fatal within a few years. Chelating agents increase renal copper excretion. Due to its many serious side effects penicillamine is no longer used and has been replaced by alternatives such as chelators like zinc (induces hepatic metallothionine to sequester hepatic copper), trientine, or, in the symptomatic phase, tetrathiomolybdate (blocks intestinal absorption of copper).[59] Zinc is the treatment of choice for asymptomatic and pregnant patients because of its efficacy and lack of toxicity,[59,60,61] whereas those with hepatic or neurological involvement receive tetrathiomolybdate.[59] Liver transplantation has been performed successfully for fulminant hepatitis.

Pregnancy is unlikely in untreated disease, because amenorrhea, subfertility, and spontaneous abortion are common. However, early copper chelation allows normal fertility and in the absence of severe liver disease, portal hypertension, or esophageal varices, pregnancy outcome is good. Estrogen induces a rise in plasma ceruloplasmin and clinical improvement or remission may occur. Discontinuing treatment may lead to relapse, presenting as a severe hemolytic crisis (requiring blood transfusion and plasma exchange) or fulminant liver failure,[62] and the fetus may suffer liver damage. Although penicillamine and trientine have a low risk of congenital malformations, zinc is the preferred chelating agent.[63] Genetic counseling should be offered.

Table 14.8 Diseases associated with Budd-Chiari syndrome

Polycythemia vera rubra

Paroxysmal nocturnal hemoglobinuria

Inherited thrombophilias
- antithrombin, protein C or S deficiency
- factor V Leiden

Malignancy

Anesthetic implications

There are very few case reports describing obstetric anesthesia in women with Wilson disease.[61] Anesthetic assessment should include a review of psychological status and evaluation of hepatic function, thrombocytopenia, coagulopathy, skin abnormalities, and neurological involvement. If esophageal varices are present, neuraxial analgesia and instrumental delivery will avoid straining and possible variceal hemorrhage.[53]

Neuromuscular blocking drugs should be used with caution and monitored because of myasthenic syndrome,[61] and careful attention to asepsis is required in the presence of bone marrow toxicity. Regional techniques are valuable, if not contraindicated, although cranial nerve involvement may mandate general anesthesia. If severe liver disease is present (see Acute liver failure), preparation for intra- and postpartum hemorrhage is advised.

Other liver diseases

Budd-Chiari syndrome

This syndrome, characterized by thrombotic occlusion of hepatic veins, is rare in pregnancy. In 105 cases, only one presented during pregnancy, but fifteen presented four days to three weeks postpartum.[64] The etiology is uncertain, but the hypercoagulable state of pregnancy may be a predisposing factor. Liver biopsy shows congestion and centrilobular liver necrosis,[1,2,3,4,54] and the clinical features include hepatomegaly, sometimes ascites, and occasionally acute liver failure. The onset may be insidious over months or acute, and diagnosis is made with Doppler flow studies, venography, or magnetic resonance imaging. Anticardiolipin antibodies may be detected and there are several associated diseases (see Table 14.8). Management is with heparin and oral anticoagulants, but the obstruction may be resistant to anticoagulation, thrombolytic therapy, and other attempts at revascularization.[1,2,3,4,54,65]

Maternal prognosis is poor. Surgical intervention for shunting is associated with high mortality,[64,65] and liver transplantation may be required.[1] Antenatal presentation is associated with a poor prognosis. In addition to the detailed assessment of liver function and the application of appropriate anesthetic principles, the implications of anticoagulation must be considered.

Peliosis hepatitis

This rare infectious disease is caused by the gram-negative bacteria genus *Bartonella*, best known because one species causes "cat scratch disease". These bacteria are widespread and cause opportunistic infection with diverse clinical manifestations, including angiomatosis, liver and spleen vasculitis, and endocarditis. Liver pathology is characterized by irregular blood-filled spaces and cystic dilation of hepatic sinusoids, sometimes with calcification. Patients may be asymptomatic, or experience complications such as portal hypertension, liver failure, or intraperitoneal hemorrhage. Cases in pregnancy and the puerperium have been reported, including immunodeficient patients.[66,67] Disease regression may occur with antibiotic treatment,[68] and successful hepatic artery embolization has been described.[67]

Autoimmune hepatitis

This chronic disease of uncertain origin may affect women of childbearing age, but pregnancy is uncommon because of associated hypothalamic-pituitary dysfunction. With immunosuppressive therapy menstruation returns and pregnancy becomes possible. The immunotolerance of pregnancy has a positive effect on disease progression, but postpartum relapse is very frequent.[69] Treatment with prednisolone is considered safe, although first trimester use is associated with a small risk of cleft palate. Azathioprine is safe throughout pregnancy.[3,27]

Hydatid disease

Hydatid disease or cystic ecchinococcosis is a parasitic disease found worldwide but most prevalent in countries in the Mediterranean, South America, Middle East, and the Pacific, where the incidence is from 1–220 per 100 000. In the USA a few hundred cases are reported each year. Primarily a disease of sheep and cattle, humans are accidental hosts, with the adult worm containing eggs transmitted in canine feces. Larvae develop in the intestine and penetrate the wall to the portal circulation and go to the liver. However, cysts also may occur in the spleen, mesentery, and pelvis, although not in the placenta, so the neonate is not exposed.[70] Cysts are often asymptomatic. Diagnosis is by ultrasound and confirmed by an indirect hemagglutination test.

The disease is rare during pregnancy, with a rate of less than 1 in 30 000 even in endemic areas, and there are only a few published case reports. It has been postulated that cysts may expand and present during pregnancy because of decreased cellular immunity.[71] Medical treatment is with antihelmintics such as albendazole and mebendazole. Drug therapy is usually reserved for recurrent disease or where surgery is impossible, but use during pregnancy is controversial.[72] Teratogenicity and embryotoxicity are reported in some animal models, although a safe dose has been determined in sheep. Antihelmintics have been used in human pregnancy without ill effect.[72] Perioperative albendazole has been successfully combined with surgery[72,73,74] to cure the disease, although the World Health Organization does not recommend surgery during pregnancy because of the risk of intra-abdominal dissemination or severe anaphylaxis from spill of cyst contents. Nevertheless, surgery may be required urgently because of cyst torsion or rupture, or to remove large cysts that obstruct labor.[70]

Liver emergencies

Hepatic rupture

There are over a hundred case reports of liver rupture in pregnancy, with trauma[75] or rupture of a subcapsular hematoma associated with severe preeclampsia being common causes. Other pathology includes rupture of intrahepatic hemangiomas, tumor, and abscess (pyogenic, amoebic, or parasitic), or in association with cocaine abuse. Most cases that complicate preeclampsia occur in late pregnancy or peripartum, and arise from an intraparenchymal hematoma in the superior and anterior sections of the right lobe, rupturing along the inferior edge of the right lobe.[3,4]

This diagnosis should be suspected in any pregnant woman who presents with RUQ pain, signs of peritoneal irritation, or hypovolemia. Diagnosis can be confirmed with a contrast CT scan, but if the patient is unstable the diagnosis may be made with abdominal ultrasound, diagnostic peritoneal lavage, or exploratory laparotomy. Both fetal and maternal mortality approach 60%.[76,77] In stable patients, a nonoperative approach involving observation and transfusion is preferred.[78] However, early surgery has helped reduce mortality and surgical options involve packing, oversewing, hepatic artery embolization or ligation, and partial lobectomy.

Acute liver failure

Acute liver failure during pregnancy results from loss of hepatocellular function as a result of a constellation of disorders such as fulminant viral hepatitis, poisoning by hepatotoxins, Wilson disease, and AFLP. Cardiovascular changes include low systemic vascular resistance and increased cardiac output. Hypoxemia results from pulmonary edema, pneumonia, pleural effusion, adult respiratory distress syndrome (ARDS), or hypoventilation associated with cerebral edema. The hepatorenal syndrome leads to oliguria, renal failure, and transient diabetes insipidus. Hypoglycemia is a consequence of defective gluconeogenesis and inadequate insulin uptake. Disseminated intravascular coagulation is present in the majority of cases.[79] Fluid and electrolyte status must be assessed regularly, and dehydration or excessive diuresis may need correction. Exchange transfusion, plasmapheresis, extracorporeal perfusion, and steroids all have a place in the treatment of acute liver failure. Despite treatment the maternal and fetal mortality is high (40% and 60% respectively, in one series).[79]

Anesthetic implications

The anesthesiologist may be required to manage an urgent delivery or liver transplantation, in a woman who is coagulopathic and encephalopathic (with restlessness, confusion, asterixis, seizures, psychosis, or coma). The choice of anesthetic technique is determined by the degree of coagulopathy and mental obtundation, with regional anesthesia preferable for C/S but rarely feasible. General anesthesia may reduce hepatic blood flow because of

controlled ventilation and the effect of inhalational anesthetic drugs. Propofol does not reduce hepatic blood flow or show altered pharmacokinetics in cirrhosis,[42] so propofol and desflurane or isoflurane, or total intravenous anesthesia with propofol, are options.[80] Caution with drug dosing is advised as prolonged responses can occur. For rapid sequence induction succinylcholine may have a less predictable duration, as may rocuronium, which undergoes hepatic metabolism. Atracurium is the neuromuscular blocker of choice because it undergoes Hoffman elimination. Nevertheless, use of a peripheral nerve stimulator is recommended as metabolic acidosis may alter the duration of neuromuscular blockers. If multiorgan failure is present or the patient is unstable at the end of surgery, postoperative ventilation and intensive monitoring are essential.

Diseases of the biliary tract

Cholelithiasis, cholecystitis, choledocholithiasis, and pancreatitis

During late pregnancy and the early postpartum period there is a predisposition to cholelithiasis, a result of increased serum lipid concentrations, slowing of bile acid excretion, and reduced small intestinal motility. Gall bladder motility returns to a prepregnant level a few days after delivery.[2,3] Despite these changes, acute cholecystitis is uncommon, with a prevalence of 1 in 1000–10 000 pregnancies.[81,82] The clinical presentation is typical, with RUQ pain and tenderness, fever, and leukocytosis, and the course of the disease is unchanged. Back pain (supported by raised serum amylase) indicates pancreatitis, which can be associated with alcohol or viral illness.[83] Pancreatitis results in long periods without oral intake, longer hospital stay, and lower neonatal birth weight. However, maternal and fetal prognoses have improved recently due to better intensive care and neonatal resuscitation.[84] The diagnosis of gallstones is often confirmed with ultrasound. Although the majority of women with acute cholecystitis are suitable for conservative management, the relapse rate is >33% and surgery may be preferable. Complications of gallstones now represent the second most common nongynecological condition requiring surgery during pregnancy, and cholecystectomy is performed at a rate of 1–8 per 10 000 pregnancies. Endoscopic retrograde cholangiopancreatography may be required for common bile duct stones. In the second trimester, cholecystectomy is associated with good maternal and fetal outcome, even when disease is severe.[82,84,85] Lead shielding of the uterus minimizes fetal exposure to radiation and anesthetic management follows usual principles. The anesthetic issues with respect to placental perfusion and gas exchange during laparoscopic surgery with pneumoperitoneum have been reviewed.[86,87]

Primary biliary cirrhosis and primary sclerosing cholangitis

Primary biliary cirrhosis (PBC) is a rare disease with prevalence of 1 in 13 000. It is diagnosed by detection of IgG antibodies to mitochondrial pyruvate dehydrogenase, or by liver biopsy. Histology shows slowly progressive destruction of intrahepatic bile ducts, portal inflammation, and scarring. Most patients are women aged 35–60 years and infertility is common, so pregnancy is rare. The disease shows a wide clinical spectrum and variable natural history, and patients are usually asymptomatic, although symptoms may include pruritus, jaundice, and fatigue. Serum ALP and GGT are raised, and aminotransferases and bilirubin may be mildly elevated.[88,89] It is not known whether pregnancy causes deterioration, although some reports describe worsening liver function in women with PBC during pregnancy.[88] Maternal and fetal outcomes are variable, with premature delivery and stillbirth described, but good outcome can be expected in well-compensated disease.[90] Management is with UDCA antenatally and after the first trimester,[91] but methotrexate is teratogenic and must be avoided. Ursodeoxycholic acid has unknown embryotoxicity but appears safe. Liver transplantation is the only definitive therapy for advanced disease.

Primary sclerosing cholangitis is another rare disease that is associated with inflammatory bowel disease. The only effective means of halting disease progression is liver transplantation. During pregnancy, pruritus may be prominent, but the course of the disease appears unaltered and neonatal outcome is usually good.[92]

Renal disease

Until recently, successful pregnancy among patients with severe renal disease was unusual, but with better medical care, this has now become commonplace. Published experience specific to the management of pregnant women with renal disease is limited, possibly because some renal diseases have little impact on obstetric and anesthetic management, while in others pregnancy is unusual. Systemic diseases that cause renal pathology, include diabetic nephropathy, hypertensive nephropathy, systemic lupus erythematosus, and various connective tissue disorders.

Kidney size is larger in pregnancy, mainly because of a 75% increase in renal blood flow. There is dilation of the renal pelvis, calyces, and ureter, more marked on the right side, probably due to a combination of hormonal factors and obstruction by the gravid uterus. The glomerular filtration rate (GFR) increases from 100 to 150 ml/min by the second trimester causing a fall in serum urea and creatinine. Hence, during pregnancy normal or slightly raised serum urea and creatinine (>80 μmol/l) indicate poor renal function. Proteinuria increases slightly and tubular reabsorption of glucose decreases, which contributes to the development of gestational diabetes in some women. Tubular reabsorption of bicarbonate also decreases, producing a compensatory metabolic acidosis in response to the respiratory alkalosis seen in pregnancy. There is increased production of vitamin D, renin, and erythropoietin by the kidney, but their effects are masked by other changes.

Chronic renal failure in pregnancy

The increase in GFR during pregnancy is attenuated with moderate renal impairment and lost with severe impairment. Chronic renal failure (CRF) is uncommon in pregnancy, occurring in 0.03–0.12% of all pregnancies in the USA.[93] Chronic renal failure

Table 14.9 Maternal complications associated with chronic renal disease

Preeclampsia
Worsening renal function
Preterm delivery
Anemia
Chronic hypertension
Cesarean delivery

is defined as a progressive decrease in GFR and is mild when the GFR > 50 ml/min, moderate if GFR is 10–29 ml/min, severe if GFR < 10 ml/min, and end-stage if the GFR < 5 ml/min. Diabetes mellitus and hypertension account for more than 50% of cases of chronic renal failure in the general population. Severe renal impairment or renal failure affects most body systems, mandating a thorough preoperative assessment.

In the woman with CRF symptoms, signs of hypertension and accelerated atherosclerosis are common. The electrocardiogram should be reviewed for signs of hyperkalemia (which may cause ventricular dysfunction and acute dysrhythmias) and for QT prolongation (which may reflect hypocalcemia). Hypoalbuminemia and low plasma oncotic pressure predispose to the development of pulmonary edema in the presence of fluid overload. A decrease in surfactant production increases the risk of postoperative atelectasis, and impaired response to infection increases the risk of pneumonia.

In CRF the concentrating ability of the kidney is impaired, leading to sodium and water retention. On the other hand, hypovolemia may result from fluid loss secondary to pyrexia, vomiting, or surgery. Hyperkalemia, hypermagnesemia, and chronic metabolic acidosis are common features. Intestinal absorption of calcium is decreased and phosphate excretion is impaired, such that hyperphosphatemia develops, calcium is deposited in the soft tissues, and osteomalacia occurs. Glucose intolerance and diabetes mellitus are common. There is an increased risk of gastric irritation and gastrointestinal hemorrhage. Nausea and vomiting are common problems in the uremic patient.

Central nervous system manifestations, such as confusion or convulsions, are late and sinister signs in CRF. Peripheral neuropathies should be documented preoperatively, especially prior to a regional block, and there is the possibility of coexisting autonomic neuropathy.

Normochromic normocytic anemia is a classic feature of CRF, although widespread use of recombinant erythropoietin has decreased the severity of chronic anemia. The platelet count may be low or normal, and while standard coagulation tests are often normal, bleeding time is frequently prolonged in uremic patients, probably because of defective von Willebrand factor.[96] Abnormal bleeding in the acute setting can be treated with D-desmethyl-arginine vasopressin (DDAVP) and possibly recombinant factor VIIa. Low serum albumin and metabolic acidosis may increase the free-drug concentration of certain drugs. The activity of drugs eliminated in part or largely by the kidneys is prolonged, mandating dose adjustment (see below).

Pathophysiology and causes of acute renal failure in pregnancy

Acute renal failure (ARF) in pregnancy is a rare event, having a reported incidence of 1 in 10 000.[1] Acute tubular necrosis and/or renal cortical necrosis are associated with severe preeclampsia, PPH, AFLP, or obstructive uropathy.[92] Acute tubular necrosis (ATN) complicates many conditions, with severe uncorrected hypotension and preeclampsia the most common causes during pregnancy. The incidence of ATN in pregnancy has fallen dramatically due to the decline in septic abortion. Acute tubular necrosis occurs as a complication in 1–2% of women with severe preeclampsia, but usually there is full recovery of renal function. Pregnant women are more predisposed to develop renal cortical necrosis. The main antecedents of renal cortical necrosis are placental abruption, preeclampsia, and amniotic fluid embolism. Hematuria is more common with renal cortical necrosis than with ATN, and a larger proportion of women with renal cortical necrosis never recover normal renal function.

Other causes of ARF include hemolytic uremic syndrome (HUS) and renal tract obstruction. Obstructive uropathy and nephrolithiasis are neither more common, nor more likely to be complicated, during pregnancy, and urinary tract stones rarely cause ARF. Ureteric stenting or percutaneous nephrostomy can be used to relieve obstruction.

Maternal and fetal outcome in renal disease

Maternal complications associated with chronic renal disease are listed in Table 14.9. The live birth rate in women with chronic renal disease ranges from 64–98% depending on the degree of renal insufficiency and presence of hypertension.[93] Women with end-stage renal failure (serum creatinine > 170 μmol/l) often experience amenorrhea or irregular menses, and are subfertile or infertile, and are likely to have an increased rate of early pregnancy loss and stillbirth. Renal function may deteriorate from the physiological stresses of pregnancy, and 40% and 66% respectively of women with moderate or severe renal impairment experience deterioration. A small proportion of those with moderate disease do not recover postpartum, but almost all women with severe impairment have persistent deterioration and one in three develop end-stage renal failure.

Maternal and fetal outcomes depend on many factors including degree of renal dysfunction at conception; the underlying disease process; and the degree of hypertension at conception or in early pregnancy. Better outcomes occur in women with mild renal dysfunction (serum creatinine <120 μmol/l) prior to pregnancy, with prepregnancy BP the most important prognostic factor. Patients with established hypertension are more likely to experience disease progression and have worse fetal outcomes. The incidence of preeclampsia among patients with mild renal disease is not greatly increased, but if serum creatinine is > 110 μmol/l the incidence is very high.

Maternal and fetal outcomes in pregnant women with renal disease have been compared with matched controls with a high-risk pregnancy but no renal impairment.[94] Women with renal

disease had higher BP during the first and third trimesters and a greater rate of pregnancy loss, mainly due to first trimester spontaneous abortion. The rate of premature delivery and C/S was similar in both groups. Diabetic patients had similar outcomes to controls, but those with hypertension had a poorer outcome, and fetal loss was more common in the presence of autoimmune disease. Focal segmental glomerulosclerosis, IgA nephropathy, and reflux uropathy were associated with the worst outcomes among those with renal disease including a high rate of fetal loss. Only 3% of women with renal disease suffer deterioration in renal function postpartum. Most of these have poor renal function and severe hypertension at the time of conception, so deterioration usually reflects natural progression of the disease.

Anesthesia for the pregnant woman with renal failure

Patients with mild renal disease, normal renal function, and no hypertension present no particular anesthetic concerns. In contrast, there are many anesthetic issues in women with end-stage renal failure, moderate to severe renal impairment, or those on dialysis. Such women should be identified as high risk early in pregnancy and appropriate monitoring and management plans established in close liaison with obstetric, nephrology, and anesthetic colleagues. The literature is devoid of cases specifically discussing obstetric anesthetic considerations in the presence of renal disease, but the following general advice can be applied.[95,96]

Maternal intravascular volume must be assessed with a view to maintaining BP, renal and placental perfusion. Large fluid or blood-volume loss may be poorly tolerated and central venous pressure (CVP) monitoring should be considered. Arterial BP monitoring is useful in cases where large blood loss is anticipated or occurs. Electrolyte disorders should be corrected.

Treatment of diabetes may require an insulin and dextrose infusion. Anemia should be sought and corrected, while taking care to avoid transfusion of patients who have adapted to low hemoglobin levels. Renal patients are prone to delayed gastric emptying, and full precautions against gastric aspiration are advisable. Drugs that are primarily excreted by the kidneys should be avoided, or the dosage altered (see Table 14.10).

Hypercarbia should be avoided because extracellular acidosis causes intracellular potassium to move into the extracellular compartment, potentially exacerbating hyperkalemia. In the presence of hypermagnesemia, nondepolarizing muscle relaxants are potentiated. Potassium release following the use of succinylcholine is not increased in renal failure, but caution is necessary in those with hyperkalemia, as normal potassium release may evoke dysrhythmias. Uremia may disrupt the blood–brain barrier, resulting in an exaggerated response to induction agents. Patients with renal failure are more prone to thrombosis, so antithrombotic therapy is frequently indicated. Nonsteroidal anti-inflammatory drugs and other nephrotoxic drugs should be avoided.

Renal patients are at increased risk of infection, so strict asepsis is required when undertaking invasive procedures. Great care must be taken of arteriovenous fistulae. A fistula should be bandaged and padded during childbirth or anesthesia. Intravenous catheters should be sited well away from a fistula, using the opposite limb whenever possible. Patients with osteomalacia are prone to fractures, especially if the patient is under regional anesthesia, so careful attention to positioning and movement is needed. Consideration must be given to the most appropriate setting for care after delivery. High-dependency care, where close monitoring of fluid and electrolyte balance can continue, is often required.

There is no evidence supporting additional benefits from regional blockade in pregnant patients with renal failure. Although an epidural hematoma has been reported in a patient with chronic renal failure,[97] epidural analgesia is commonly used for patients undergoing renal transplantation.[98] Epidural insertion is generally considered safe in renal patients, with the usual provisos in relation to anticoagulants, such as low molecular weight heparin. It may be difficult to assess the coagulation status of renal patients who present in labor or require urgent delivery, as platelet count and coagulation tests are often normal. Thromboelastography has been used in parturients with thrombocytopenia to assess global clotting function,[99] although a risk–benefit assessment is required on an individual basis. Ideally, patients with renal impairment should be identified early in pregnancy, providing time to perform specific tests and to obtain the opinion of a hematologist.

The maximum plasma concentration or time to peak concentration of bupivacaine is not significantly altered in patients with renal failure.[98] The onset of subarachnoid blockade may be faster, the dermatomal spread increased by one or two segments, but the duration of the block is reduced.[100] Possible explanations include the effects of a hyperdynamic circulation and acidosis on the binding and pharmacokinetics of local anesthetics.

Specific renal diseases

Urinary tract infection

Bacteruria is present in 3–7% of pregnant women and urinary tract infection (UTI) occurs in 25% of pregnancies. Acute pyelonephritis complicates up to 1% of pregnancies.[101] This is often secondary to dilatation of the renal tract and urinary stasis. Women with recurrent UTI should be monitored closely with renal ultrasound. Prophylactic antibiotic therapy may reduce further infections and preserve renal function. Preterm labor may be triggered by UTI.[102]

Pyelonephritis is often due to *Escherichia coli* and some women present with septic shock, requiring intensive care. Other serious complications include pulmonary edema, ARDS, hemolysis, and thrombocytopenia. It is postulated that low colloid osmotic pressure and plasma fibronectin concentration during pregnancy may explain an apparent increase in vulnerability to pulmonary complications.[103]

A rare complication of obstruction and UTI is nontraumatic rupture of the renal tract. In a series of 14 cases,[104] eight had a rupture of the collecting system and six had rupture of renal parenchyma. Patients complained of abdominal pain, most

Table 14.10 Adjustment of drug dosages in renal failure

Fentanyl	No change in dose required.
Alfentanil	No change in dose required.
Remifentanil	No change in dose required.
Morphine	Metabolites morphine 3- and 6-glucuronide accumulate and cause prolonged effect.
	Not cleared by hemofiltration or dialysis.
Diamorphine	Metabolites accumulate and cause prolonged effects.
Meperidine	Metabolite (normeperidine) accumulates and may cause seizures.
Codeine	Accumulation of morphine metabolites may cause prolonged effects.
Dihydrocodeine	Accumulation of morphine metabolites may cause prolonged effects.
Dextropropoxyphene	Accumulation can cause unwanted effects.
Buprenorphine	Metabolites do not cause undesirable effects.
Oxycodone	Decrease dose by half in severe renal impairment.
Propofol	No change in dose required. Glucuronide metabolites accumulate, but have no unwanted effects.
Thiopental	No change in dose required.
Ketamine	No change in dose required.
Volatile anesthetic agents	Some renal metabolism but mainly pulmonary excretion, so generally safe to use.
	All decrease GFR but have no effect on renal autoregulation.
	Renal blood flow maintained with halothane, isoflurane, and desflurane.
	Sevoflurane should be avoided because of potential renal toxicity of fluoride ion.
Succinylcholine	No change in dose required.
Atracurium	No change in dose required.
Vecuronium, Rocuronium	Best avoided, because all have partial renal excretion.
Pancuronium	If used, may have prolonged action and neuromuscular block must be monitored.
Neostigmine	Excretion delayed, similar to nondepolarizing muscle relaxants.
Diazepam	Metabolites accumulate and may cause prolonged effects.
Midazolam	Reduce dose if GFR < 10 ml/min.
Paracetamol	Accumulates, but normal dose suitable.
NSAID	Avoid, as they cause a rapid decrease in GFR in patients with renal disease. Also cause hyperkalemia, edema and hypertension.
	Not removed by hemofiltration or dialysis.
Tramadol	Active metabolites may accumulate.
	Reduce dose or increase dosing frequency in severe renal impairment.
Butyrophenones	No change in dose required.
Phenothiazines	No change in dose required.
Clonidine	No change in dose required.
Glyceryl trinitrate	No change in dose required.
Beta-blockers	Down-titrate dose.
Alpha-blockers	No change in dose required.
Calcium channel antagonists	No change in dose required.
Methyldopa	Excreted unchanged in urine.
	Prolonged duration of action.
Antidysrhythmics	No change in dose required.
Digoxin	Reduce dose and monitor serum concentration.
Ranitidine	Reduce dose by half when GFR < 10 ml/min.
Metoclopramide	No need to reduce dose after single administration only.
Penicillins	Reduce dose by half when GFR < 10 ml/min.
Cephalosporins	Reduce dose by half when GFR < 10 ml/min.
Oxytocin	Rapidly inactivated by the liver.
	Caution with infusions, which can cause water intoxication.
Ergometrine	Metabolized in the liver and mainly excreted in the feces.
	No change in dose required.
Low molecular weight heparin	Reduce dose when GFR < 30 ml/min.

GFR = glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drug

severe on the side of the rupture. Five patients required nephrectomy, one died before surgery, and two suffered intrauterine fetal death.

Reflux nephropathy and calculi

Reflux nephropathy and renal scarring are important causes of renal impairment in pregnancy. Scarring occurs in 50% of women who have bacteruria in pregnancy, and UTI is more common if vesico-ureteric reflux is present. Renal stones are no more common in pregnancy, because inhibitors such as magnesium, citrate, and nephrocalcin are present in greater quantity. Apart from an increase in UTI, stones do not have an adverse impact on pregnancy. Nevertheless, treatment may be difficult, because xanthine oxidase inhibitors for urate stones, and d-penicillamine for cystine stones, are best avoided, especially in the first trimester. There are inadequate data on the safety of lithotripsy during pregnancy. It has been suggested that some women with severe vesico-ureteric reflux might benefit from ureteric reimplantation prior to pregnancy and that early dialysis may improve fetal outcome.

Ureteric obstruction and subsequent hydronephrosis, in the absence of renal calculi, can occur from pressure by the expanding uterus. This can cause severe maternal flank pain and may require ureteric stent placement to relieve the obstruction. Cystoscopy and stent placement can be performed under spinal anesthesia. Figure 14.1 shows an x-ray of an indwelling left ureteric stent in a woman with ureteric compression and hydronephrosis at 36 weeks' gestation.

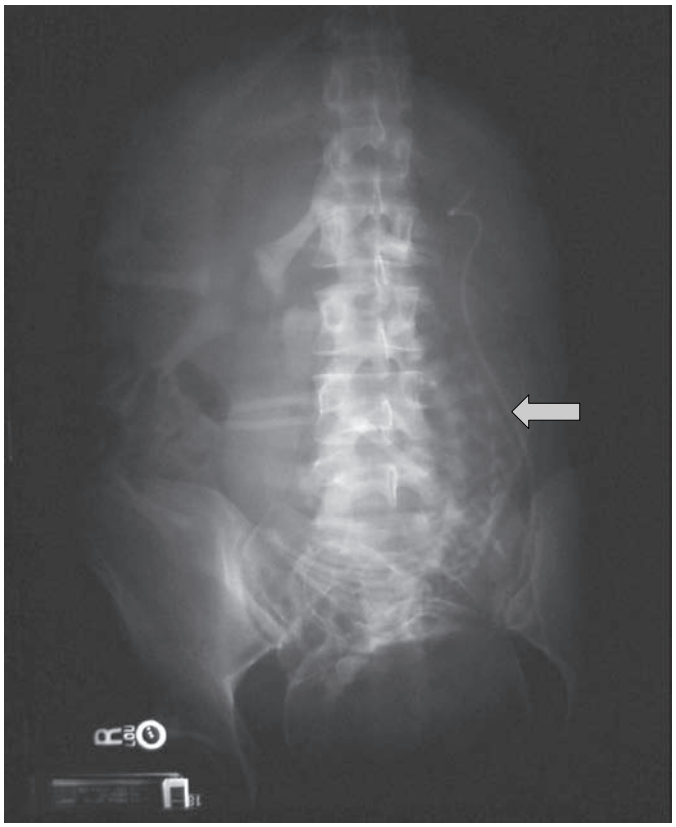

Figure 14.1 Plain x-ray of abdomen and pelvis in a woman at 36 weeks' gestation with severe flank pain associated with left ureteric obstruction and hydronephrosis. A left ureteric stent was placed under spinal anesthetic. The stent and a fetus with a head engaged in the pelvis are clearly seen. The arrow points at the left ureteric catheter. (See color plate section.)

Glomerulonephritis

The label "glomerulonephritis" encompasses a range of conditions in which the glomerulus is inflamed (see Table 14.11), either as a primary renal disease or part of a systemic illness. Diagnosis and division into pathological subcategories requires renal biopsy, which has a low complication rate in pregnancy.[105] Patients present with nephrotic syndrome (proteinuria, edema, and hypoalbuminemia); nephritic syndrome (oliguria, edema, hypertension, proteinuria, hematuria, and renal impairment); or proteinuria, hematuria, or hypertension alone. Pregnancy outcome is determined by the severity of renal impairment. Patients with lupus nephritis have a high rate of fetal loss and deterioration in renal function, particularly if the disease is active.[106] Postinfectious glomerulonephritis is unusual in pregnancy, but can occur after streptococcal throat infection.[107] It presents with an acute nephritic syndrome, characterized by severe hypertension and edema. The prognosis is good and treatment is mainly supportive, including antihypertensive drugs and diuretics.

Vasculitic diseases

Wegener granulomatosis and Churg-Strauss syndrome are small vessel vasculitides associated with antineutrophil cytoplasmic antibodies (ANCA). Blood-vessel walls become inflamed and necrotic, leading to fever, night sweats, and weight loss. Patients with Churg-Strauss syndrome develop worsening asthma, eosinophilia, and granulomatous lesions, but as the disease mostly affects males, pregnancy is rare.[108] Women with Wegener granulomatosis show signs of upper respiratory tract disease, including epistaxis and nasal bridge collapse,[109] and ARF may develop.

Treatment of these conditions involves high-dose cyclophosphamide and corticosteroids. Plasma exchange may improve outcome but mortality is high. For patients who enter remission within four to six weeks, the ANCA status may become negative. Pregnancy is best avoided until the disease is in remission, since pregnancy may cause a relapse. The placenta appears unaffected by the vasculitic process, so fetal mortality and morbidity is low.

Hemolytic uremic syndrome (see Chapter 17)

Hemolytic uremic syndrome (HUS) is characterized by nonimmune hemolytic anemia, thrombocytopenia, and renal failure. The incidence of HUS during pregnancy is estimated as 1 in 25 000. Hemolytic uremic syndrome in pregnancy is associated with a high perinatal mortality rate.[110] For further details please refer to Chapter 17.

Goodpasture syndrome

Goodpasture syndrome is an autoimmune disease in which antiglomerular basement membrane antibodies are directed against collagen IV in basement membranes. It is characterized by glomerulonephritis and pulmonary hemorrhage. It is mainly a disease of young men, or men and women over 60 years of age. Younger patients present with hemoptysis, anemia, proteinuria, and red-cell casts in the urine. Management includes glucocorticoids (to control pulmonary hemorrhage), immunosuppression (to prevent further renal damage), and intermittent plasmapheresis (to clear circulating antibasement membrane antibodies from the circulation). The disease usually displays a chronic course, with recurrence or complete clearance of the antiglomerular basement membrane antibody following treatment. Autoimmune antibodies can be deposited in the placenta.

Goodpasture syndrome is rare in pregnancy but cases have been reported.[111,112] Pregnancy may be complicated by glucocorticoid-induced hyperglycemia, hemodialysis, intermittent plasmapheresis, immunosuppressant therapy, and preterm birth.[111] Successful pregnancy was reported in a woman following kidney transplantation for end-stage renal failure. This patient had no pulmonary involvement but experienced preeclampsia and graft rejection postpartum, probably from poor compliance with immunosuppressive therapy.[112]

Inherited renal disorders

Autosomal dominant polycystic kidney disease (ADPKD)

In autosomal dominant polycystic kidney disease (ADPKD) renal cyst enlargement leads to destruction of surrounding renal tissue, resulting in renal failure, and bilateral kidney enlargement.[113] Presenting symptoms include hypertension, UTI, hematuria, loin pain, and renal calculi, but the first manifestation is often end-stage renal failure. Cysts may be found in the

Table 14.11 Glomerulonephritis

Condition	Clinical presentation	Renal prognosis	Treatment
Minimal change nephropathy	Often presents in childhood with nephritic syndrome. Occasionally secondary to NSAID use or malignancy.	Rarely progresses to renal dysfunction.	>90% respond to high-dose corticosteroids.
Focal segmental glomerulosclerosis	Nephritic syndrome. Hypertension, microscopic hematuria, impaired renal function are associated.	50% patients develop end-stage renal failure within ten years.	High-dose corticosteroids. ACE inhibitor to reduce proteinuria. Statin for hyperlipidemia.
Membranous nephropathy	Asymptomatic proteinuria or nephritic syndrome. Microscopic hematuria and hypertension are associated. May have IgG complex deposition. Idiopathic or secondary to NSAID, gold, penicillamine, carcinoma of breast, bronchus, colon.	Impaired renal function may occur.	May resolve completely if causative agents withdrawn. 25% patients have resolution of proteinuria. High risk of thrombotic effects.
IgA nephropathy	Most common cause of hematuria worldwide. Deposition of IgA in glomerulus. Similar glomerular injury is seen in Henoch Schonlein purpura, with vasculitic rash and arthritis.	Good prognosis in patients with no proteinuria, hypertension, or renal impairment. 25% of patients with proteinuria of 1 g per 24 h develop end-stage renal failure.	Immunosuppression not helpful. No proven treatment.
Mesangiocapillary glomerulonephritis	Uncommon. Three sub-types. Associated with activation of the complement cascade. Proteinuria, hematuria, hypertension, impaired renal function.	Up to 50% develop renal failure within ten years.	
Focal necrotizing glomerulonephritis	Acute nephritic syndrome (acute renal failure, hematuria, proteinuria, cellular casts in urine). With pulmonary hemorrhage is known as Goodpasture syndrome. ± ANCA. May represent form of small vessel vasculitis.	Usually presents with acute renal failure.	Plasma exchange to remove circulating antibodies. Corticosteroids and cyclophosphamide.

NSAID = nonsteroidal anti-inflammatory drugs; ACE = angiotensin converting enzyme; ANCA = antineutrophil cytoplasm antibodies

liver and pancreas and other extrarenal complications include intracranial aneurysms, mitral valve prolapse, and diverticular disease. Clinical symptoms and evidence of renal dysfunction usually appear in later life, but pregnancy outcomes of 235 women with ADPKD have been described.[114] A decline in renal function was associated with increasing multiparity and although fertility was unaffected, ectopic pregnancy rates were higher. Twenty five percent of affected women developed hypertension during pregnancy, 11% preeclampsia, and there was an increased risk of subsequent chronic hypertension. Normotensive women with normal renal function generally had uncomplicated pregnancies. Increases in intracranial pressure should be avoided or attenuated because intracranial aneurysms may be present, although rupture has not been reported. Epidural analgesia with controlled instrumental delivery, or elective C/S, is a good management option.

Tuberous sclerosis

Tuberous sclerosis is an autosomal dominant multisystem disorder in which hamartoma formation affects the skin, brain, and heart in particular.[115,116] Features include seizures, mental retardation, facial angiofibromas, and renal angiomyolipomas. Only 23 pregnancies in women with tuberous sclerosis were identified in 2005, and two were complicated by bleeding into renal cysts.[115]

Alport syndrome

Alport syndrome is an inherited disease characterized by hematuria, proteinuria, progressive renal failure, and sensorineural deafness.[116] Some patients also develop lenticonus of the anterior lens capsule, retinopathy, and rarely mental retardation and leiomyomatosis. A variety of related syndromes reflect the many genetic variations – examples are X-linked, recessive, dominant,

benign familial hematuria, and nail-patella syndrome. Renal failure often develops by 30 years of age.

Bartter syndrome

Bartter syndrome is a rare, autosomal recessive renal tubular disorder characterized by severe hypokalemia, metabolic alkalosis, hyperaldosteronism, and normotension.[117] Clinical manifestations include growth restriction, muscle weakness, cramps, polyuria, and polydipsia. The limited number of case reports during pregnancy[117,118,119,120,121] suggest good maternal and fetal outcome, provided serum potassium and magnesium levels are normal.

Obstetric and anesthetic management should be directed toward maintenance of serum potassium levels, using intravenous potassium supplements and magnesium supplements, as required.[119] In the nonpregnant population, angiotensin converting enzyme (ACE) inhibitors are effective at maintaining normokalemia, but are contraindicated during pregnancy because of the potential for both teratogenic (hypocalvaria) and fetal effects (renal failure, oliguria, and demise). Potassium sparing diuretics such as amiloride and spironolactone are safe and good alternatives.[120] Sodium loss is a feature of Bartter syndrome, so patients are prone to hypovolemia. Regional block should be established carefully, with preparation to prevent and treat hypotension. Marked resistance to vasopressors, especially angiotensin II and norepinephrine, has been reported,[119] and baroreceptor responses are often abnormal. If blood loss is anticipated, CVP monitoring is advisable. Hyperventilation should be avoided because hypocapnia may lead to a reduction in serum potassium. Effective regional analgesia for laboring patients is recommended.

Gitelman syndrome

Gitelman syndrome is a milder form of Bartter disease that rarely progresses to end-stage renal disease. Prolonged QT interval has been described,[122] so drugs prolonging the QT interval should be used with caution and with appropriate monitoring (see Chapter 2).

Renal tubular acidosis

Renal tubular acidosis is characterized by inadequate renal hydrogen-ion excretion, despite normal glomerular filtration. Type 1 renal tubular acidosis is inherited in an autosomal dominant manner and affects the distal tubules, while Type 2 affects the proximal tubules. Both result in hyperchloremic metabolic acidosis, with a normal anion gap.

There are few reports of renal tubular acidosis and pregnancy. One describes two pregnancies, both complicated by hypertension[123] although there were no adverse maternal or fetal sequelae.

Renal replacement therapy (dialysis) in the pregnant woman with renal disease

Although still uncommon, the incidence of pregnancy in women who receive chronic hemodialysis is 1–7%, and 30–50% of these women will have a successful pregnancy outcome. Improvements in dialysis regimens and the widespread use of erythropoietin have led to less anovulation and infertility such that many women have regular menses.[124] Diagnosis of pregnancy can be difficult, as small amounts of human chorionic gonadotrophin (HCG) are secreted by somatic cells and are not cleared by the kidney, producing elevated levels in the nonpregnant state. Longstanding proteinuria can give false positive pregnancy tests.

Dialysis may be required in women with renal impairment who become pregnant and then develop end-stage renal failure. Some recommend commencing dialysis when the GFR falls below 20 ml/min. Protein restriction can be relaxed and may improve maternal and fetal nutrition. Better outcomes are generally seen in women who reach later gestations before requiring dialysis, and in those who have been on dialysis for shorter periods before becoming pregnant.

Preterm delivery occurs in about 50% of cases, and for uncertain reasons polyhydramnios is a common feature.[124] Attention has been directed to improving outcome by increasing the time spent on dialysis, with the best results found in those who are dialyzed for 20 or more hours per week. Maternal hypertension occurs in 40–80% of dialyzed women and abruption, anemia, and antepartum hemorrhage may occur. About 10% of women develop preeclampsia, and hypertension worsens in 20%. Increased red blood cell production during pregnancy is outstripped by the increase in plasma volume, so hemoglobin concentration usually falls. Up to a two-fold increase in erythropoietin dose may be required to maintain an adequate level of hemoglobin.

Successful pregnancy among patients on continuous ambulatory peritoneal dialysis (CAPD) has also been reported.[124] Continuous ambulatory peritoneal dialysis may be complicated by premature labor precipitated by peritonitis. A theoretical advantage over hemodialysis is that the fetus is exposed to a more stable environment, with fewer rapid fluid and electrolyte shifts, but obstetric outcomes are similar. The C/S rate is approximately 50%, with many cases urgent because of premature rupture of membranes or abruption. The anesthesiologist should liaise with the nephrologist to determine current fluid and electrolyte status and time of last dialysis.

Summary

Although the most common cause of hepatic dysfunction and jaundice in pregnant women is viral hepatitis (A, B, C, D, E, and G viruses), there are a number of uncommon diseases unique to pregnancy that are significant causes of mortality and morbidity. The most important are intrahepatic cholestasis of pregnancy and AFLP. Liver dysfunction is also a feature of many multisystem disorders, the most important of which is preeclampsia. The obstetric anesthesiologist has a role to play in antenatal, intrapartum, and postpartum multidisciplinary care and should have a sound understanding of the pathophysiology of these conditions. Regional analgesia and anesthesia is often valuable, but dysfunction of the coagulation system may preclude neuraxial techniques. General anesthesia should be modified to address considerations relevant to patients with impaired liver function. Women with cirrhosis, portal hypertension, acute liver failure, or hepatic rupture pose major anesthetic challenges.

Although ARF in pregnancy is a rare event, acute tubular necrosis and/or renal cortical necrosis are associated with several common diseases of pregnancy, including severe preeclampsia and PPH. Acute renal failure is also associated with a number of less common diseases, such as AFLP and obstructive uropathy. Maternal and fetal outcomes in women with renal disease depend on factors such as degree of renal dysfunction at conception, the underlying disease process, and the degree of hypertension. Improvements in medical care now result in successful pregnancy outcomes, even among women receiving renal replacement therapy. These women should be identified as high risk early in pregnancy, and managed in a tertiary center with appropriate monitoring and care plans established in liaison with perinatologists and nephrologists. The general principles relevant to anesthesia for patients with renal impairment or failure can be applied during pregnancy.

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15 MALIGNANT HYPERTHERMIA

M. Joanne Douglas

Introduction

Malignant hyperthermia (MH) is an inherited disorder of skeletal muscle, which produces a hypermetabolic syndrome when susceptible individuals (MHS) are exposed to the triggering anesthetic agents.[1] The known triggering agents are volatile anesthetics (halothane, isoflurane, enflurane, sevoflurane, and desflurane)[1,2,3,4,5,6,7] and succinylcholine. They act by causing a sudden increase in intramyoplasmic calcium (Ca^{2+}), which results in increased skeletal muscle metabolism.[8] The diagnostic characteristics of acute MH are acidosis (combined metabolic and respiratory), muscle dysfunction (increased creatinine kinase [CK], myoglobinuria, rigidity, hyperkalemia) and evidence of inheritance. Although called malignant hyperthermia, marked elevation of temperature is often a late sign but may occur as early as 15 minutes following initiation of a volatile anesthetic agent in fulminant MH.[9] The increase in intracellular Ca^{2+} may be due to a mutation in the ryanodine receptor such that the threshold stimulus for Ca^{2+} release is lowered or a defect in modulation at the receptor.[9]

In a study of MH in susceptible swine, Ryan *et al.* demonstrated the sequence of events during a reaction.[8] An increase in free myoplasmic Ca^{2+} precedes the increase in end-tidal CO_2, followed by a decrease in arterial oxygen saturation (SaO_2). These changes are followed by tachycardia and lastly hyperthermia. Dantrolene reversed these in the same order. Hypermetabolism (increased end-tidal CO_2) begins when the intracellular Ca^{2+} increases above 0.6–0.7 μM, while muscle contracture and rigidity occur with a level above 1.0 μM.[8]

MH and inheritance

MH is inherited in an autosomal dominant fashion with variable penetrance.[10] The RyR1 gene (responsible for the ryanodine receptor in skeletal muscle) appears causal for MH in pigs[11] and in some humans.[12,13,14,15,16,17,18,19,20] Linkage studies attempting to isolate a single responsible gene in humans have demonstrated that human MH is multigenic.[20,21] Correlation between DNA testing and results of the caffeine halothane contracture test (CHCT, also known as the in vitro contracture test, IVCT) has not been conclusive.[13] A possible reason for this is the lack of 100% specificity for the CHCT.[22] A recent study identified defects in the RYR1 gene that were causal for 70% of MH/MHS individuals and the authors recommend the use of denaturing high-performance liquid chromatography as a valid screening method.[23] Mutation analysis has recently become available in the United States.[24] There is a report describing the use of molecular genetic analysis of umbilical cord blood to diagnose MH susceptibility in the newborn of a known MH susceptible mother.[25] The authors suggest that pregnant women with a history of MH in themselves or their family be offered the option of molecular genetic testing of umbilical cord blood.

Clinical picture of MH

The classic picture of MH is that of an increase in end-tidal CO_2, increased oxygen consumption (may result in cyanosis or decreased SaO_2), acidosis (metabolic and respiratory), and muscle destruction (increased CK, myoglobinuria, hyperkalemia). These result in tachycardia, tachypnea, unstable blood pressure (BP), dysrhythmias, and an increased temperature. Muscle rigidity (either masseter muscle rigidity [MMR] at the time of intubation or generalized rigidity) is another sign. Approximately 10% of MH cases are fulminant and require rapid diagnosis and aggressive treatment.[26]

While much debate has focused on the significance of MMR, especially in children, most consider its development a warning sign of impending MH. While some use the terms MMR and trismus interchangeably, Hannalah and Kaplan have classified MMR as an inability to open the mouth fully but intubation is possible, while trismus is the total inability to open the mouth and intubate.[27] They consider both to be an early sign of MH and recommend discontinuing anesthesia unless required urgently. Some cases of incomplete relaxation (increased force is required to open the mouth), may be a normal variant of response to succinylcholine.[28] Under these circumstances, some advocate continuing anesthesia with nontriggering agents and close monitoring.[29] In one series of adult patients with MMR, 25% tested positive for MH using the caffeine halothane contracture test.[30]

In pigs, hyperthermia[31] can trigger MH in the absence of anesthetic triggers, while prior hypothermia attenuates MH.[32,33] Elevated CO_2, hyperkalemia, exogenous Ca^{2+}, and adrenergic agents do not increase the chance of MH.[34,35,36,37]

Differential diagnosis

Diseases that mimic MH include sepsis, neuroleptic malignant syndrome (NMS), cocaine overdose, hyperthyroidism,[9] and 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") toxicity.[38] Some congenital disorders can result in a hyperthermic response during anesthesia, which is not MH. These include osteogenesis imperfecta, familial dysautonomia (Riley Day Syndrome), and arthrogryposis multiplex congenita. Myopathies that result in a hypermetabolic picture in association

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with masseter rigidity include the myotonias (congenita, fluctuans, myotonic dystrophy, paramyotonia congenita and Schwartz-Jampel syndrome, periodic paralysis), central core disease, mitochondrial myopathies,[9] King (King-Denborough) syndrome,[39,40] and muscular dystrophy. It is important to exclude these disorders by a neurological examination and electromyography (EMG) testing, as the CHCT may be positive. A response to dantrolene does not prove the diagnosis of MH.[9]

In order to aid the clinical definition of MH and research on MH, Larach *et al*. developed a clinical grading scale to predict MH susceptibility.[41] This scale assigns points to various indicators, based on their predictive value for MH. The total score indicates the qualitative likelihood for MH.

Treatment of MH

Treatment of an MH episode consists of stopping the volatile anesthetic agent, hyperventilation with 100% oxygen, administration of dantrolene (2.5 mg/kg initially, and up to 10 mg/kg) and instituting other measures to treat acidosis, hyperkalemia, dysrhythmias, promote urine output, and cool the patient.[9] The changing of the anesthetic machine to a "clean" machine is not considered a high priority. Dantrolene is effective and may have to be repeated until the reaction is controlled. Research indicates that very low concentrations of dantrolene open isolated Ca^{2+} release channels whereas higher concentrations block the channel.[42] This may be the mechanism of mild hypermetabolism following treatment of an MH episode and may be important in myopathies (other than MH) that produce a similar hypermetabolic picture.[43] Creatinine kinase levels should be assessed every six hours for 24 hours following an alleged episode to assess rhabdomyolysis.

At the time of a reaction the diagnosis of MH is made on clinical grounds and subsequently confirmed by the CHCT. Reviews of experience in administering anesthetic triggering agents to patients who have tested negative for MH indicate that this is probably safe.[44,45,46]

Malignant hyperthermia and obstetrics

Strazis and Fox reviewed the worldwide literature on all reported cases of MH and found that MH predominated in the pediatric and male population.[47] Previous uneventful anesthesia was found in 20.9% and absent positive family history 75.9% of the time. Congenital defects and musculoskeletal surgical procedures were associated clearly with MH. This study has confirmed the apparent lower incidence of MH in pregnancy than in the rest of the population. Reported cases in pregnancy are rare,[48,49,50,51,52,53] with most reports relating to management of the MHS parturient.[54,55,56,57,58,59] This apparent lower incidence may be due to regional anesthesia being used more frequently in obstetrics for procedures of shorter duration. There are two reports of obstetric and anesthetic management of parturients with King (King-Denborough) syndrome, a nonspecific myopathy with MH-susceptibility and dysmorphic features similar to Noonan syndrome.[38,40] There is one report of maternal masseter rigidity and neonatal fasciculations that was secondary to central core disease, a disease associated with MH.[60] As noted earlier in this chapter, a newborn was diagnosed with MH susceptibility using molecular genetic analysis of umbilical cord blood.[25]

Anesthesia for an MHS parturient

Ideally the patient with known MH susceptibility will be seen in consultation prior to her admission to hospital. This allows a full discussion of the implications of the diagnosis on the management of her labor and delivery. As the greatest risk relates to general anesthesia (GA), insertion of an epidural catheter early in labor will allow it to be used for analgesia as well as for an operative delivery, should the need arise.

All of the local anesthetics are safe. There were questions in the past about the use of adrenergic agents in MHS patients, but evidence in humans suggests that epinephrine and norepinephrine are not triggers for MH.[36] There is an overwhelming adrenergic response during an MH crisis and epinephrine should not be used at that time. In doses used clinically, ephedrine is probably safe although an in vitro study of ephedrine, in significantly greater amounts than would be used clinically, found that it increased halothane-induced contractures.[36] Other agents commonly used in obstetrics, such as narcotics, ketamine, nitrous oxide/oxygen in a 50:50 mixture are safe (see Table 15.1).

When anesthesia is required for an emergency cesarean section (C/S) and a functioning epidural is not in place the preferred technique is spinal anesthesia. Although insufficient time may be present in which to adequately preload the patient with intravenous fluids, a recent study suggests that administration of a fixed volume is not essential.[61] Rarely, regional anesthesia may fail or there is a contraindication to its use and so GA must be used. In this situation the triggering agents must be avoided. In

Table 15.1 Safety of drugs for the MHS parturient

Induction agents	thiopental, propofol, ketamine, etomidate, benzodiazepines: all are safe
Muscle relaxants	**succinylcholine: not safe**; atracurium, vecuronium, rocuronium, mivacurium, pancuronium: all safe
Reversal agents	neostigmine, physostigmine (+ atropine, glycopyrrolate): all safe
Inhalational agents	nitrous oxide: safe; **isoflurane, halothane, sevoflurane, desflurane: not safe**
Analgesics for labor/delivery	all narcotics: safe; local anesthetics (+ epinephrine): safe
Oxytocics	oxytocin PGF2alpha, ergot preparations: safe, may mimic MH. **Avoid during a reaction unless specifically indicated**.
Tocolytics	B-sympathomimetics: safe, may mimic MH; nitroglycerin, magnesium sulphate: safe
Cardiovascular drugs	ephedrine: probably safe; epinephrine, norepinephrine: Safe[a]

[a] Do not use during a reaction due to the overwhelming adrenergic activity

animal studies, thiopental does not induce MH and has some protective effect.[62] Other induction agents, propofol, benzodiazepines, and ketamine, are also safe. The greatest risks to all parturients during GA are pulmonary aspiration of gastric contents and difficult or failed intubation. Therefore, it is essential to adequately assess the airway prior to induction of GA. Where possible, prophylactic H-2 receptor blockers and metoclopramide should be administered to neutralize gastric acid and promote gastric emptying. Sodium citrate, given minutes before induction, raises the pH of gastric contents. Succinylcholine is contraindicated in MHS patients even though it is the preferred agent for intubation in obstetric patients due to its rapid onset and, if difficulties are encountered with intubation, rapid offset. The intermediate acting nondepolarizing muscle relaxants such as atracurium, vecuronium, and rocuronium are favored for the MHS parturient. Adequate intubating conditions can be achieved rapidly with rocuronium providing the induction dose of thiopental is increased to 6 mg/kg and a dose of 0.9–1.0 mg/kg of rocuronium is used (the normal recommended intubating dose is 0.6 mg/kg).[63]

Some recommend the use of prophylactic dantrolene in the setting of GA, but I feel that it is not necessary providing one avoids the known anesthetic triggers. It should be readily available in the operating room and all personnel (nurses and anesthesiologists) should be familiar with its use. The use of warm sterile water (40°C) to dilute the dantrolene allows for more rapid reconstitution.[64] As an alternative to volatile anesthetics to obtund awareness during surgery, the use of a small dose of midazolam or diazepam following anesthetic induction or after delivery, is a reasonable option. Of greatest importance is the monitoring of the parturient, irrespective of the type of anesthesia. This includes the use of the routine monitors of automatic blood pressure, EKG, pulse oximetry, end-tidal CO_2 (for GA), and, if concern arises about the development of a reaction, arterial cannulation in order to serially monitor blood gases (theoretically a venous gas is of greater value), electrolytes, and other parameters. Temperature should be monitored in two sites: esophageal or rectal and axillary (close to large muscle groups).[65]

One can rapidly eliminate volatile agents from a standard anesthetic machine (convert it to a "clean" machine).[66,67] As noted above, turning the vaporizers off and running high-flow oxygen in the case of a developing crisis is sufficient until other measures have been undertaken, e.g. confirmation of diagnosis and administration of dantrolene. Then attention can be paid to removing the vaporizers, changing the circuit, and replacing the CO_2 absorbent. In the elective situation, remove the vaporizers, flush the anesthetic machine with a high flow of oxygen (10 liters) using the ventilator for 20 minutes, replace the fresh gas outlet hose, use a new disposable circuit, and change the CO_2 absorbent.[9]

Differential diagnosis of MH during labor and delivery

Several drugs used in obstetrics may mask or mimic the signs and symptoms of MH. These include the ergot preparations, beta-sympathomimetics (ritodrine, terbutaline), and the prostaglandins. The ergot preparations and beta-sympathomimetics can produce tachycardia and dysrhythmias, while the prostaglandins can alter arterial oxygen saturation[68] and increase temperature.[69,70] Oxytocin is safe[71] and is the preferred agent to increase uterine tone in the MHS parturient. Obviously in the face of life-threatening hemorrhage when oxytocin is ineffective one may have to use an ergot preparation or a prostaglandin. Two of the "hallmark" signs of MH are tachycardia and increased temperature, and these are common in obstetrics due to pain, infection (chorioamnionitis), and anxiety (see Table 15.2).

Table 15.2 Common causes of tachycardia and fever in the parturient

Cause	Tachycardia	Fever
Sepsis (e.g. chorioamnionitis)	++	+ to ++++
Dehydration	+/−	+
Pain, anxiety	+++	−
Epidural analgesia	−	+

Anesthetic management of the MH-negative mother with a possible MH-positive fetus

If one of the parents of a fetus is MHS the fetus has a 50% chance of inheriting the gene for the syndrome, as MH is inherited in an autosomal dominant manner. Concern is often raised about anesthetic management of an MH negative mother where the father of the fetus is MHS. The anesthetic agents cross the placenta and theoretically the fetus could develop MH if triggering agents are used in the mother.[72,73] It probably is advisable to avoid the known anesthetic triggers, but to date there has been only one reported case of an infant with rigidity at birth. Malignant hyperthermia was considered a possible diagnosis but there was no follow-up.[74]

Dantrolene and pregnancy

Dantrolene crosses the placenta.[75] In the gravid ewe, during an infusion rate of 2.2 mg/kg/h, the fetal to maternal ratio is 0.48.[75] This is similar to that reported by Morison in two parturients following oral dantrolene.[76] Prophylactic oral administration produces minor maternal side effects and no adverse fetal or neonatal effects.[77] There is one reported case of postpartum uterine atony following dantrolene administration,[78] but recent evidence suggests that this is probably not due to the dantrolene itself.[79] At a cumulative concentration of 20 g/ml of dantrolene Shin *et al.* found depression of spontaneous uterine muscle contractility, but this also occurred with mannitol. The authors felt that dantrolene, per se, did not have any effect on isolated uterine smooth muscle and that any reaction was due to its solvent vehicle, mannitol.[79] Lecithin-coated microcrystals dissolve more rapidly (no mannitol) and form an effective preparation in the treatment of MH in swine.[80] Although this preparation may eliminate the problem of potential uterine hypotonia it is not yet available.[81]

Levels of dantrolene have been measured in breast milk following its acute administration for an MH crisis. The half-life for dantrolene in breast milk was nine hours and the authors concluded that it was safe for the newborn to breast feed two days following discontinuation of intravenous dantrolene.[53]

Summary

Although episodes of MH have rarely been reported during pregnancy, there is no evidence that pregnancy alters the response to triggering agents. The increased use of regional anesthesia for labor and delivery and C/S may partly explain the apparent lower incidence from that in the overall population. The obstetric anesthesiologist must be prepared to diagnose and treat an unexpected episode of MH and to manage a woman who is MHS who is admitted in labor. Management of an acute MH episode is similar to that in the nonobstetric patient. With the advent of molecular genetic diagnosis it may be possible to diagnose MH susceptibility in a newborn using umbilical cord blood.

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16 RARE ENDOCRINE DISORDERS

J. M. Mhyre and L. S. Polley

Introduction

Endocrinopathies can complicate pregnancy with adverse maternal and fetal effects. Pregnancy can mask or mimic signs and symptoms of endocrine disease making diagnosis difficult.

Thyroid disease

Hyperthyroidism

Hyperthyroidism is relatively common in the general population and occurs in 2 of 1000 pregnancies.[1] Graves disease causes 80–95% of cases of hyperthyroidism in pregnancy. Other causes include thyroiditis, toxic adenoma, multinodular goiter, viral thyroiditis, and tumors of the pituitary or ovary. Human chorionic gonadotropin (hCG), which peaks between 8 and 14 weeks, weakly stimulates thyroid stimulating hormone (TSH) receptors, and in some cases leads to transient hyperthyroidism associated with hyperemesis gravidarum.[2] High levels of hCG with clinical hyperthyroidism may also be seen with gestational trophoblastic disease and multiple pregnancies.

Subclinical hyperthyroidism occurs in pregnancy (1.7% of all screened women), and, in the general population, has long-term sequelae such as osteoporosis, cardiovascular morbidity, and progression to overt thyrotoxicosis.[3] These women have suppressed TSH but normal free thyroxine (T4) levels. African-American and parous women are more likely to be affected, but there are no adverse pregnancy outcomes. Identification of subclinical hyperthyroidism and treatment during pregnancy is unwarranted.[3]

Thyrotoxic crisis (thyroid storm)

Thyroid storm is the most serious complication of hyperthyroidism. This exaggerated hypermetabolic state occurs in 2% of pregnancies complicated by hyperthyroidism with a reported maternal mortality rate of 15% and a 24% rate of stillbirth. Thyroid storm is often precipitated in women with Graves thyrotoxicosis by common obstetric complications such as hemorrhage, severe preeclampsia, and sepsis.[4]

Clinical features

Pregnant women with thyroid storm demonstrate high fever, dehydration, nausea, vomiting, and diarrhea. The cardiovascular system is hyperdynamic with tachycardia, dysrhythmia, and high-output congestive heart failure (CHF). Neurologic symptoms include skeletal muscle weakness, altered mental status, and seizures, which may progress to coma and death.

Because the consequences of thyroid storm are life threatening, management should commence once the diagnosis is suspected. Laboratory tests of thyroid function typically require at least eight hours of analytic time, and are of little value in distinguishing thyroid storm from untreated hyperthyroidism. Leukocytosis may be present, but may also signal an underlying infection that precipitated the metabolic derangement.

The differential diagnosis includes malignant hyperthermia (MH), pheochromocytoma, neuroleptic malignant syndrome, and sepsis.

Fetal effects

Thyroid storm may result in preterm labor, premature birth, preeclampsia, and intrauterine fetal demise. If the fetus is alive when the mother presents with thyroid crisis, then fetal heart rate (FHR) tracing may show tachycardia, decreased or absent beat-to-beat variability, and late decelerations. These abnormal FHR patterns generally improve with correction of the maternal metabolic derangement.

Management and anesthetic implications

Pregnant women with thyroid storm should be admitted for invasive central monitoring because they are often dehydrated and require vigorous hydration with crystalloids in the face of potential cardiac dysfunction. Glucose and electrolyte abnormalities must be corrected and fever treated with cool intravenous (i.v.) fluids, a cooling blanket, and acetaminophen. Aspirin should be avoided because it may increase circulating active T3 and T4 by reducing protein binding.

Propylthiouracil (PTU) inhibits the iodination of thyroglobulin in the thyroid, and blocks the peripheral conversion of T4 to T3. Potassium iodide and sodium iodide block the release of thyroid hormone from the thyroid gland. Propranolol inhibits the adrenergic effects of thyroid hormone and blocks the peripheral conversion of T4 to T3. In cases with significant cardiac dysfunction or bronchospastic airway disease, a titratable esmolol infusion or diltiazem may be preferred. Dexamethasone also decreases thyroid hormone release and blocks the peripheral conversion of T4 to T3. A treatment protocol is summarized in Table 16.1.

Surgical procedures should be postponed until the metabolic derangements of thyroid storm are controlled. If the mother's condition is unstable, emergent cesarean section (C/S) for fetal indications may jeopardize the lives of both mother and fetus. As previously mentioned, the fetal condition generally improves with correction of the maternal metabolic derangement.

Following the diagnosis and institution of therapy, a search should be made for underlying precipitating conditions,

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Table 16.1 Management protocol for pregnant women with thyroid crisis

- Hospitalization and intensive nursing care
- Invasive hemodynamic monitoring with evaluation for heart failure and dysrhythmia
- Fetal monitoring: ultrasound, biophysical profile, or nonstress test
- Hydration and correction of glucose and electrolyte abnormalities
- Adrenergic blockade titrated to a 25% reduction in heart rate:
  propranolol 1 mg/min i.v. up to 10 mg, may repeat q 4–6 h
  or esmolol 500 μg/kg/min i.v. load over 1 min, then 25–200 μg/kg/min
  or diltiazem 0.25 mg/kg load over 2 min, then 5–15 mg/h
- PTU 1000 mg po, then 200 mg q 6 h
- Iodide solution starting 1 hour after giving PTU:
  supersaturated potassium iodide (SSKI) 30 gtt po, then 5–10 gtt q 6 h
  or sodium iodide 0.5 g i.v. in 1 l of NS over 12 h
  or lithium carbonate 300 mg po q 6 h if hypersensitive to SSKI
- Dexamethasone 2 mg i.v. q 6 h up to 8 mg
- Consider
  dantrolene
  plasma exchange
  spinal anesthesia to the fourth dermatomal level
  L-carnitine
- Evaluate for precipitating causes

Adapted from Wissler, R. N. Endocrine disorders. In Chestnut, D. H. (ed.), *Obstetric Anesthesia: Principles and Practice*, 3rd edn. Philadelphia: Elsevier Mosby, 2004; p. 747.

including infection (e.g. pyelonephritis, chorioamnionitis), thromboembolic disease, stroke, diabetic ketoacidosis, or hypoglycemia. Normal labor, hemorrhage, and preeclampsia may also precipitate thyroid storm.

Anesthetic management includes careful evaluation of the airway, recognizing that significant enlargement of the thyroid gland can obstruct the trachea or a bronchus. Retrosternal goiter may not be apparent on physical examination, and may require computerized tomography (CT) to make the diagnosis. If the potential for significant airway obstruction exists, an awake fiberoptic intubation is the airway management technique of choice.[5]

Nonpharmacologic methods to reduce patient anxiety should be used preferentially. However, patient anxiety may contribute to hemodynamic lability, and small, titrated doses of midazolam may be necessary. In doses less than 0.02 mg/kg, midazolam does not appear to produce neonatal sedation or respiratory depression, or maternal amnesia for delivery.

Preoperative twelve-lead electrocardiogram (EKG) and perioperative cardiac rhythm monitoring are recommended. Invasive cardiovascular monitoring may be helpful to guide fluid management and adrenergic blockade, particularly if high-output CHF or significant dysrhythmias are present. Drugs that promote tachycardia should be avoided including ketamine, anticholinergics, sympathomimetics, and pancuronium.[6] A perioperative esmolol infusion may be useful to control cardiovascular responses to sympathetic stimulation, but should be used with caution in the presence of CHF or asthma.

With careful management, either general or regional anesthesia is acceptable for C/S that is performed when the maternal condition has been stabilized. Regional anesthesia can be administered safely if there are no signs of high-output cardiac failure,[7] and may be therapeutic for thyroid storm. Continuous epidural anesthesia has the advantage of slower onset of sympathetic blockade, with time to position the patient and to administer fluid boluses and small doses of phenylephrine (20–40 μg) to prevent hypotension. High levels of circulating thyroid hormones increase beta-adrenergic receptors,[8] and thus epinephrine should not be added to local anesthetic solutions because of the risk of an exaggerated circulatory response.

A diagnosis of thyroid storm during general anesthesia (GA) is made on the basis of the history and intraoperative vital signs, which demonstrate a hypercatabolic state. In such cases, the differential diagnosis should include MH,[9] sepsis, and pheochromocytoma.

Regardless of anesthetic technique, postoperative monitoring is essential because a crisis can occur postpartum in the recovery unit.[10]

Hypothyroidism

Overt hypothyroidism complicates up to 3 of 1000 pregnancies.[1,11] Most women affected by hypothyroidism experience chronic anovulation and increased rates of fetal loss, so the true prevalence of hypothyroidism in pregnancy is difficult to assess. Myxedema, the most severe complication of hypothyroidism, is rare and, if untreated, can lead to myxedema coma.

The etiology of hypothyroidism includes autoimmune thyroiditis (Hashimoto disease), subtotal thyroidectomy, radioiodine therapy, and primary hypothyroidism. Worldwide, the leading cause of hypothyroidism is iodine deficiency. Hypothyroidism occurs in 10% of all type I diabetics.

Clinical features

Clinical features in women of childbearing age consist of abnormal menses, conception, and fertility. Also seen are diminished deep tendon reflexes, fatigue, hair loss, dry skin, and brawny edema. Diagnosis is confirmed by a low free T4 serum level and an elevated TSH.

Hypothyroidism is associated with an increased risk of preeclampsia, placental abruption, intrauterine growth restriction (IUGR), prematurity, stillbirth, emergency C/S for nonreassuring FHR pattern, acquired von Willebrand (VW) syndrome,[12] and postpartum hemorrhage. The blood dyscrasia appears to be related to an impaired release of VW factor that resolves once the hypothyroidism is corrected. No case reports have linked hypothyroidism to epidural hematoma. Other serious maternal end-organ effects include anemia, cardiomegaly, cardiomyopathy, conduction abnormalities, bradycardia, and cardiac stroke volume reduction. Maternal thyroid hormones play a significant role in early neurologic development, and maternal hypothyroidism between the 7th and 20th week of gestation places the fetus at risk for impaired neurologic development and neonatal mental retardation.[13]

Thyroid replacement therapy with levothyroxine 0.1 mg/day has no known adverse fetal effects if euthyroid hormone levels are achieved.[14] The aim is to lower TSH levels to 0.5–1.5 mIU/l.[11] Excess thyroid supplementation may increase risk for spontaneous abortion or IUGR.[15] Both levothyroxine and endogenous T4 and T3 cross the placental barrier to enter the fetal circulation; however, there are marked maternal to fetal gradients of all three. At delivery, maternal serum free T4 and T3 concentrations are twice those in cord serum. In cases of fetal thyroid agenesis, intrauterine neurologic development is often normal because the small amount of maternal T4 transferred to the fetus contributes to T3 concentrations in the fetal brain minimizing the effects of fetal hypothyroidism.

Subclinical hypothyroidism refers to early or mild thyroid hypofunction with slightly high TSH (4–10 mIU/l) and normal T4 and T3 levels.[11,16] The consequences of subclinical hypothyroidism in the general population are minimal.[17] However, pregnancies in women with subclinical hypothyroidism are three times more likely to have placental abruption and two times more likely to have preterm labor (< 34 weeks).[16]

Anesthetic implications

Laboring women who begin their pregnancy with severe hypothyroidism are at increased risk for urgent C/S for nonreassuring FHR pattern, regardless of their thyroid status at term. Therefore, epidural placement in labor may be helpful in facilitating a rapid transition to surgical delivery. For patients rendered euthyroid during the antepartum period, no major modifications of either general or regional anesthesia are required.

Patients who remain severely hypothyroid present a number of potential anesthetic problems. Firstly, there may be excess sensitivity to induction agents, opioids, and sedatives. Minimal doses of sodium thiopental or ketamine are given for emergency C/S using GA. In some women, nitrous oxide alone may cause unconsciousness. Secondly, cardiac depression and bradycardia may be worsened by the effects of depressant drugs such as induction agents and volatile anesthetics. Fortunately, hypothyroid patients appear to respond normally to i.v. fluids and exogenous catecholamines. Nevertheless, invasive hemodynamic monitoring may be indicated, particularly in the presence of hypovolemia and abnormal baroreceptor reflexes. Thirdly, reduced skeletal muscle activity may impair postoperative respiratory effort and may increase sensitivity to neuromuscular blocking agents. A peripheral nerve stimulator may not be reliable in the severely hypothyroid patient.[18] Fourthly, abnormal respiratory control mechanisms and impaired central neurologic responses to hypoxia and hypercarbia mandate monitoring of oxygen saturation and end-tidal CO_2 throughout the perioperative period. Finally, the management of the hypothyroid patient is further complicated by acquired VW syndrome, altered metabolism and inactivation of drugs, primary adrenal insufficiency, electrolyte and free-water clearance abnormalities, hypoglycemia, and delayed gastric emptying.

Regional anesthesia appears to be safe provided that volume and cardiac status are carefully monitored and maintained. Neurologic examination prior to block placement may reveal any preexisting neurologic weakness or paresthesias. If acquired VW disease is suspected, desmopressin 0.3 μg/kg given i.v. over ten minutes has been shown to acutely correct the coagulation defect. Metabolism of amide local anesthetics may be slowed, and some authors have speculated an increased risk for local anesthetic toxicity, although none has been demonstrated. The stress of labor or surgery may unmask reduced adrenal cortical function, warranting steroid supplementation.

Thyroid dysfunction and drugs

Various drugs affect thyroid function through their actions on production, secretion, transport, and metabolism of thyroid hormones (see Table 16.2).[19]

Long-term therapy with cytokines in patients with chronic inflammatory disorders or tumors may result in thyroid dysfunction. Interferon alpha has been associated with antithyroid microsomal antibodies in 20% of patients, and transient hypothyroidism, hyperthyroidism, or both may result.

Amiodarone is not recommended in the first trimester of pregnancy because it has the potential to cause hypothyroidism and hyperthyroidism in the neonate in addition to congenital defects (see Chapter 2). Amiodarone causes characteristic changes in thyroid function in euthyroid individuals because of its iodine content and a direct toxic effect on thyroid parenchyma.[20]

Neonatal thyroid dysfunction

Neonatal hyperthyroidism develops in 1–5% of the offspring of women with Graves disease, as a consequence of the transplacental passage of thyroid-stimulating immunoglobulin (TSI). Women rendered euthyroid by thyroid gland ablation before pregnancy may continue to produce TSI. The fetus exposed to TSI may experience IUGR, goiter, and tachycardia, and as a neonate, may demonstrate tachycardia, irritability, weakness, and hyperactivity. Neonatal hyperthyroidism is usually transient, lasting one to five months, and resolves in proportion to the half-life of immunoglobulin (IgG).

Neonatal hypothyroidism without goiter can occur when women with Graves disease produce TSH-binding inhibitory immunoglobulin (TBII). These antibodies cross the placenta, bind fetal TSH, and cause transient fetal hypothyroidism. Affected neonates are at risk for bradycardia and IUGR.

Neonatal hypothyroidism with goiter can result when maternally administered antithyroid drugs including propylthiouracil, methimazole, and iodine, cross the placenta, suppress the fetal thyroid gland, and stimulate fetal TSH.

Fetal goiter may often be diagnosed by prenatal ultrasound, and fetal hormone levels may be safely monitored using intrauterine umbilical blood sampling.[21] Effective therapy is available, including the intra-amniotic injection of levothyroxine for fetal hypothyroidism and the maternal administration of antithyroid drugs for fetal hyperthyroidism. If unrecognized, fetal goiter may interfere with vaginal delivery or obstruct the neonatal airway.

Table 16.2 Drugs that alter thyroid function

A. **Drugs that may potentiate or exacerbate hyperthyroidism**
   1. **Drugs that increase TSH secretion**
   Iodine, Lithium
   Dopamine antagonists, Tricyclic antidepressants
   2. **Drugs that increase thyroid hormone secretion**
   Iodide, Amiodarone
   3. **Drugs that may exacerbate symptoms of hyperthyroidism**
   Sympathomimetics, Anticholinergics
   Ketamine, Pancuronium
B. **Drugs that may potentiate hypothyroidism**
   1. **Drugs that decrease TSH secretion**
   Dopamine, Glucocorticoids, Octreotide
   2. **Drugs that decrease thyroid hormone secretion**
   Iodine, Lithium, Amiodarone
   3. **Drugs that displace T4 and T3 from TBG**
   Furosemide, Phenytoin, Sulfonylureas, Mefenamic acid, Fenclofenac, Salicylates
   4. **Drugs that block gastrointestinal absorption of thyroid hormone**
   Ferrous sulfate, Aluminum hydroxide, Sucralfate, Cholestyramine
   5. **Drugs that increase hepatic T4 and T3 metabolism**
   Phenobarbital, Rifampin, Phenytoin, Carbamazepine
   6. **Drugs that decrease T4 to T3 conversion**
   Propylthiouracil, Amiodarone, B-adrenergic-antagonists, Glucocorticoids
C. **Drugs that alter thyroid hormone measurement**
   1. **Drugs that increase TBG concentration**
   Estrogens, Heroin, Methadone, Fluorouracil
   2. **Drugs that decrease TBG concentration**
   Androgens, Anabolic steroids, Slow-release nicotinic acid, Glucocorticoids

Previously adapted from Surks, M. I. & Sievert, R. Drugs and thyroid function. *N. Engl. J. Med*. 1995; 333: 1688. Copyright 1995 Massachusetts Medical Society. All rights reserved.
Updated using Nader, S. Thyroid disease and pregnancy. In RK Creasy, R. K., Resnik, R. & Iams, J. D. (eds.), *Maternal–Fetal Medicine: Principles and Practice*, 5th edn. Philadelphia: Saunders, 2004; pp. 1063–81.

Table 16.3 Diabetic ketoacidosis complicating pregnancy: incidence and fetal mortality rates

Period	Incidence	Fetal mortality
1950–79	18/277 (7.9%)	5/18 (27.7%)
1971–90	11/635 (1.73%)	2/9 (22%)
1976–81	51/227 (22%)	18/51 (35%)
1986–91	9/301 (3%)	1/9 (10%)
1985–95	11/520 (2%)	1/11 (9%)
1991–01	11/2025 (0.5%)	3/11 (27.3%)

Table adapted from Kamalakannan, D., Baskar, V., Barton, D. M. & Abdu, T. A. M. Diabetic ketoacidosis in pregnancy. *Postgrad. Med. J.* 2003; **79**: 454–7.

Pancreas

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is a medical emergency, requiring immediate treatment.[22] Data collected since 1985 shows a 0.5–3% incidence of DKA among all diabetic pregnancies, with a fetal loss rate of 9–27%. (see Table 16.3) Pregnant women with previously undiagnosed diabetes may present in DKA. Precipitating events include hyperemesis gravidarum, serious infection, insulin pump dysfunction, and neglect of care. Treatment of premature labor with corticosteroids and/or ß-sympathomimetics can also precipitate DKA.

Clinical features

Signs and symptoms vary depending on the degree and stage of metabolic derangement. Symptoms include polyuria, polydipsia, marked fatigue, nausea, vomiting, abdominal pain, and dyspnea. Signs include evidence of dehydration, hyperventilation, breath with a "fruity" odor, and altered mental status that can progress to coma. Hypotension with tachycardia indicates significant dehydration and electrolyte depletion. Mild hypothermia is usually present, so normothermia or hyperthermia should raise suspicion of infection.

The triad of hyperglycemia, ketonemia, or ketonuria, and an anion gap metabolic acidosis are pathognomonic for DKA (see Table 16.4). It usually occurs in the later stages of pregnancy and is also seen in newly presenting type 1 diabetics. The onset of DKA in pregnancy can be at lower blood sugar (BS) levels and can occur more rapidly than in nonpregnant women.[23] Hence, normoglycemia does not rule out DKA in pregnancy since up to one-third of pregnant women in DKA present with BS levels below 200 mg/dl. Significant ketonemia and an anion gap may be present with mild acidosis (pH 7.30–7.35) if the DKA is early in its clinical course. Leukocytosis as high as 25 000/µl with a left shift may occur with or without associated infection.

Differential diagnosis of DKA

If the patient is acidotic, other causes of anion gap metabolic acidosis include lactic acidosis (serum lactate above 5 mmol/l), uremic acidosis (blood urea nitrogen [BUN] $>$ 200 mg/dl) and drug-induced acidosis associated with a history of salicylate, methanol, ethylene glycol, or paraldehyde ingestion. Other ketotic states include alcoholic ketoacidosis and starvation ketoacidosis. Patients with alcoholic ketoacidosis will likely present with a history of alcohol ingestion and a disproportionate increase in ß-hydroxybuterate compared with acetoacetate. Starvation ketosis is rare, but may be more common among women with hyperemesis gravidarum.[24] The acidosis is typically mild (pH $>$ 7.3). A known diabetic with altered mental status should raise suspicion for hypoglycemic coma, hyperosmolar coma, central neurologic event, pharmacologic effects, infection, and sepsis. Sepsis and lactic acidosis may coexist with DKA.

Management

For both maternal and fetal well-being, DKA should be stabilized before delivery is attempted. Dehydration, associated with DKA,

Table 16.4 Diagnostic criteria for diabetic ketoacidosis

- Acidosis with blood pH < 7.3
- Anion gap $[Na^+ - (K^+ + Cl^-) > 10$ mEq/l]
- Serum bicarbonate < 18 mEq/l
- Ketonemia or ketonuria (acetoacetate and ß-hydroxybuterate)

may affect uteroplacental blood flow and combined with acidosis and ketonemia, may result in fetal demise. There may be a nonreassuring FHR pattern, with late decelerations and decreased or absent beat-to-beat variability. Once dehydration, acidosis, and electrolyte imbalance are corrected, the FHR often reverts to a normal pattern.

Treatment includes correction of dehydration, acidosis, hyperglycemia, and electrolyte imbalance. Initial hydration consists of one to two liters of isotonic saline over one to two hours to restore intravascular volume. Following saline hydration, sufficient crystalloid is administered to maintain adequate renal and uteroplacental blood flow, as evidenced by good urine output and an improved FHR pattern. The approach often requires six or more liters of fluid in the first 24 hours. A central venous pressure catheter may be helpful for guiding volume replacement.

Insulin should not be given until initial serum electrolyte values are obtained and rehydration has begun. After a bolus of 10 U of i.v. insulin, a continuous infusion is begun at an initial rate of 0.1 U/kg per hour. Once the BS falls below 250 mg/dl, the insulin infusion is decreased to 0.05 U/kg per hour, and a dextrose infusion is started (100 ml/h of 5% dextrose in normal saline). Hourly BS checks should confirm a steady decrease of 50–70 mg/dl per hour. If BS remains elevated, then ensure adequate volume replacement prior to increasing the insulin infusion rate. Potassium is added if the level is < 5.0 mEq/l and if the urine output is adequate. Bicarbonate replacement is appropriate only if the pH falls below 6.90. An underlying cause of the DKA, such as infection, should be sought and treated. Endotracheal intubation may be necessary if coma is present.

Hypoglycemic coma

Pregnant women with type 1 diabetes are particularly susceptible to severe hypoglycemia (SH), especially in the first trimester.[25] The risk of SH and hypoglycemic coma is increased if there is a history of SH before pregnancy, there is a longer duration of diabetes, and if the HbA1c is ≤6.5%.[25] In a group of 84 women with type I diabetes receiving intensive insulin therapy, 34% experienced at least one episode of significant hypoglycemia resulting in seizures, loss of consciousness, coma, injury, i.v. glucose, or glucagon treatment. Episodes peaked between 10 and 15 weeks, and became increasingly rare as pregnancy progressed.[26] In a second group of 82 gestational diabetics after 24 weeks' gestation, episodes of asymptomatic hypoglycemia (BS levels < 50 mg/dl lasting over 30 minutes) were identified in 63% of insulin-treated patients, 28% of glyburide-treated patients, and none in diet-controlled patients.[27] Hypoglycemia is possible during labor, particularly if effective regional anesthesia has eliminated the counter-regulatory stress hormones associated with pain,[28] and if the patient has fasted for an extended period of time. Other causes of hypoglycemia are summarized in Table 16.5.

Table 16.5 Causes of hypoglycemia in diabetic pregnant patients

Hyperinsulinism
Excess activity
Anorexia
Abnormal counterregulatory responses
Anti-insulin antibodies
Antibodies to insulin receptors
Impaired absorption of insulin
Impaired intake (morning sickness, diarrhea, etc)
Fetal death
Factitious insulin use
Increased insulin sensitivity (first trimester)

From: Reece A. E., Homko C. H. & Wiznitzer A. Hypoglycemia in pregnancy complicated by diabetes mellitus. *Clin. Obstet. Gynecol.* 1994; **37**: 50.

Clinical features

Hypoglycemic coma may be preceded by irritability, tachycardia, nausea, diaphoresis, and maternal confusion.[29] Significant hypoglycemia (i.e. BS levels < 30 mg/dl) can lead to coma, seizures, and death. The immediate evaluation of a pregnant woman with altered mental status should include an assessment of vital signs and the BS level. Other causes of altered mental status include hyperglycemia with or without ketonemia, infection, central neurologic event, and pharmacologic effects.

Management

Fortunately, maternal hypoglycemia has little adverse effect on the fetus with no evidence that it is teratogenic.[26,29,30] Mild to moderate hypoglycemia is not associated with an increase in the frequency of nonreassuring FHR patterns.[29] Severe hypoglycemia resulting in seizures and/or coma, however, can indirectly affect fetal well-being.

If the patient is unable to swallow, the fastest treatment is i.v. administration of 25 ml of 50% glucose. Glucagon 1 mg i.v. or i.m. (intramuscular) requires 15 to 30 minutes to achieve a response. Serum glucose should then be rechecked, particularly if mental status fails to improve.

Stiff-joint syndrome (diabetic scleroderma)

Chronic hyperglycemia may lead to glycosylation of tissue proteins that can limit joint and soft tissue mobility. For this reason, type I diabetics are at risk for difficult intubation, temporomandibular joint dysfunction, and limited cervical spine mobility. Other tissues may also be involved. In one case report, anterior spinal artery syndrome developed after epidural anesthesia in a

pregnant patient with poorly controlled diabetes. According to the authors, the injection of a large volume of epidural solution (35 ml) into the noncompliant epidural space may have compressed the vascular supply to the spinal cord.[31] Other potential complications include restrictive pulmonary disease, difficult i.v. access due to thickened skin, and poorly compressible arm tissues leading to erroneously high noninvasive blood pressure (BP) readings.

Hyperglycemic hyperosmolar state

Hyperglycemic hyperosmolar state (HHS) is far less common than diabetic ketoacidosis. There has been one case report of HHS in a pregnant woman who had severe preeclampsia, but no previous history of diabetes. This woman reverted to a normoglycemic state after delivery.[32]

Hyperglycemic hyperosmolar state is characterized by serum osmolality > 310 mOsm/kg, BS levels > 600 mg/dl, and normal blood pH (> 7.3). In this disease process, hyperglycemia leads to profound osmotic diuresis, dehydration, and hyperosmolality. Coma can occur if osmolality exceeds 320–330 mOsm/kg. Hyperglycemic hyperosmolar state is typically precipitated by an event such as infection, therapy with glucocorticoids, stroke, pulmonary embolism, or recent operation. As with DKA, stabilization of the metabolic derangements, particularly dehydration, should precede delivery. Intubation for airway protection may be necessary.

Anesthetic considerations for patients with diabetes

The timing of delivery is determined jointly by the obstetrician and anesthesiologist to ensure that the patient's condition is optimal. The preanesthetic evaluation should be completed as early as possible to allow assessment and correction of acid-base status, and fluid and electrolyte abnormalities. Serious metabolic derangements should be managed before attempting delivery, even if fetal status is not reassuring. Because of the potential for stiff-joint syndrome and difficult intubation, a careful airway examination is essential prior to any anesthetic intervention.

If nonpharmacologic methods of pain control do not provide adequate relief in labor, continuous epidural analgesia is beneficial. Pain can lead to stimulation of the hypothalamic-hypophyseal axis, causing excess release of catecholamines, which oppose insulin activity. Effective regional anesthesia decreases circulating levels of catecholamines, reducing the potential for critical decreases in uteroplacental blood flow in patients with chronic uteroplacental insufficiency. Abrupt onset of regional anesthesia may precipitate hypoglycemia in a fasted diabetic woman, so a BS should be checked if diaphoresis or dizziness develop after neuraxial block.[28]

If a C/S under GA is planned, women with stiff-joint syndrome may benefit from awake fiberoptic intubation. If significant tissue turgidity is present, concerns with neuraxial block include the possibility of noncompliance of the epidural space. In such cases, a combined spinal–epidural technique with low-dose spinal anesthesia may be preferred over epidural anesthesia, because of the smaller volume of anesthetic solution.

Labor has a glucose-lowering effect and rapid changes in BS may occur. For many gestational diabetics, no insulin is required once labor is established. For type I diabetics, a continuous infusion of insulin and dextrose in labor improves maternal glucose control and limits the risk of neonatal hypoglycemia. Blood sugar and potassium (K^+) should be checked every 30–60 minutes for any actively laboring patient on an insulin infusion. Insulin infusions should be administered through a dedicated i.v. line as blood products, in particular, will break down insulin enzymatically. Normal saline should be used for acute administration of i.v. fluids, because rapid infusions of lactated Ringer's or dextrose solutions may precipitate hyperglycemia.

Pituitary

Normal pregnancy stimulates hyperplasia of the lactotrophic cells in the pituitary.[33] As a result, previously asymptomatic women with pituitary adenomas may develop symptoms of pituitary enlargement during pregnancy, including headache, visual disturbance, and diabetes insipidus (DI). Computed tomography and magnetic resonance imaging (MRI) are helpful for tracking growth of the pituitary gland through pregnancy. Differentiating between pituitary disorders requires endocrinologic evaluation or transphenoidal biopsy, because radiologic appearance does not necessarily differ between types of adenoma.

Prolactinoma

Prolactinomas are pituitary adenomas that oversecrete prolactin, leading to amenorrhea, infertility, galactorrhea, and hyperprolactinemia. Dopamine receptor agonists, including bromocriptine and cabergoline, suppress prolactin secretion and improve conception rates.[34] Bromocriptine appears to be safe in pregnancy, although asymptomatic women discontinue therapy once pregnancy is confirmed. Data are less extensive for cabergoline, but preliminary evidence does not suggest any adverse fetal effects.[35]

Women with macroadenomas (≥10 mm) are more likely than those with microadenomas (< 10 mm) to present with symptoms of pituitary enlargement during pregnancy (23% versus 1.3%).[36] If symptoms develop, headaches usually precede visual changes, with a mean onset time of 14 weeks' gestation. In such cases, therapy with bromocriptine can be continued in pregnancy to control symptoms and reduce pituitary size. Adjunctive glucocorticoids accelerate resolution of visual symptoms. Patients who fail to improve on bromocriptine may benefit from cabergoline,[37] radiation therapy, or transphenoidal hypophysectomy.

Anesthetic implications

Pregnant women with prolactinoma should be evaluated for symptoms of increased intracranial pressure (ICP), DI, and visual disturbances. In asymptomatic women, there are no anesthetic implications. For parturients with symptoms, MRI or CT of the sella tursica is used to measure pituitary enlargement and to look for increased ICP. Women with increased ICP who expect to

deliver vaginally may benefit from regional analgesia and a shortened second stage to minimize the physiologic effects of pain and pushing. Great care must be taken to avoid inadvertent dural puncture with a large-bore epidural needle in those women with raised ICP.

Acromegaly

Acromegaly is due to excess secretion of growth hormone by the anterior pituitary in adults. Only about 100 cases of acromegaly in pregnancy have been reported.[38] Women with acromegaly may experience infertility or amenorrhea, but pregnancies do occur naturally or with the help of reproductive technology.[39] Pregnancy is associated with normal pituitary expansion due to lactotrophic hyperplasia. In pregnant women with acromegaly, this may result in compression of the optic chiasm with visual field deficits. Other complications of acromegaly, particularly glucose intolerance, hypertension, and peripheral nerve compression, may also worsen during pregnancy. Pregnancy in acromegalic women usually has a normal course leading to a normal delivery. Growth hormone does not appear to cross the placenta, and aside from maternal glucose intolerance with the potential for neonatal hypoglycemia, there are no known fetal effects of maternal acromegaly.[39]

In symptomatic patients during pregnancy, first-line therapy consists of bromocriptine until the fetus is mature. If symptoms do not improve, then transphenoidal surgery in pregnancy may be necessary. Somatostatin analogues are an alternative to surgery, although their safety in pregnancy is not firmly established.[40]

Anesthetic implications

Potential anesthetic complications include difficult mask ventilation and difficult endotracheal intubation.[41] In a series of 128 nonpregnant patients, 10% had difficult intubation where external laryngeal pressure alone did not improve the laryngoscopic view.[42] Therefore, awake fiberoptic intubation should be considered. A small endotracheal tube diameter may be necessary to avoid airway edema with postoperative airway obstruction.

Given the risk for hypertension, left ventricular (LV) dysfunction, and ischemic heart disease, a careful cardiovascular history, preoperative EKG, and perioperative cardiac rhythm monitoring are warranted. Preoperative echocardiogram or invasive cardiac monitoring may be helpful if symptoms of cardiomyopathy are present.

A careful neurologic examination should precede neuraxial blockade because acromegaly has been associated with peripheral neuropathy, cauda equina syndrome, and spinal canal stenosis. We were unable to locate a case report of lumbar epidural catheter placement in an obstetric patient with acromegaly. Further anesthetic implications of acromegaly are listed in Table 16.6.

Table 16.6 Anesthetic considerations for acromegaly

Difficult airway:
- overgrowth of the tongue, epiglottis, mandible, pharyngeal tissues, and vocal cords
- recurrent laryngeal nerve palsy due to overgrowth of the cartilaginous structures, which stretch the nerve
- glottic narrowing and subglottic stenosis

Peripheral neuropathy
Glucose intolerance
Hypertension
Dysrhythmia
Ischemic heart disease
Osteoarthritis: spinal canal stenosis
Skeletal muscle weakness

Adapted from: Stoelting, R. K. & Dierdorf, S. F. Endocrine diseases. In *Anesthesia and Co-Existing Disease*, 4th edn. Philadelphia: Churchill Livingston, 2002: pp. 395–440.

Cushing disease

In Cushing disease, a pituitary adenoma overproduces adrenocorticotropin hormone (ACTH). This in turn stimulates the adrenal glands to overproduce cortisol, leading to Cushing syndrome. Cushing syndrome refers to the group of symptoms that arise from excessive exposure to steroid hormones. Women with Cushing disease have Cushing syndrome, and the systemic effects and anesthetic considerations of Cushing syndrome are discussed in the section on adrenal disorders.

Nelson syndrome

Nelson syndrome may develop when a patient with Cushing disease is treated with bilateral adrenalectomy without adequate treatment of the primary pituitary lesion. The pituitary adenoma will continue to produce ACTH leading to hyperpigmentation, and may expand leading to mass effects including visual field changes, headache, and DI. Amenorrhea is common; however, several case reports of pregnancy are available in the literature.[43,44,45] When treating parturients with Nelson syndrome, it is important to: (1) evaluate for symptoms of increased ICP or local mass effects from pituitary hypertrophy, (2) monitor intravascular fluid volume and electrolyte disturbances from DI, and (3) provide appropriate steroid supplementation including stress-dose steroids during labor and delivery.

Diabetes insipidus

Diabetes insipidus is either caused by insufficient antidiuretic hormone (central DI) or by insensitivity of the renal tubules to antidiuretic hormone (nephrogenic DI). Diabetes insipidus may be associated with pregnancy because the placenta produces vasopressinase, an enzyme that metabolizes vasopressin (ADH).[46] Women with preeclampsia, fatty liver of pregnancy, or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome may accumulate vasopressinase, leading to

secondary DI.[47] Vasopressinase levels decline rapidly after delivery, with resolution of DI by the first or second postpartum day. Alternative causes include head trauma, Sheehan syndrome, or expanding pituitary lesions. There is a case of a pregnant woman with an occluded ventriculoperitoneal shunt resulting in increased ICP, injury to the pituitary stalk, and central DI.[48]

The incidence of DI is up to 4 cases per 100 000 pregnancies. The main diagnostic features are polyuria, polydipsia, thirst, and hypotonic urine. Because oxytocin is produced in the same hypothalamic nuclei as vasopressin, some patients may benefit from perinatal oxytocin supplementation during labor or postpartum. Dehydration, hyperosmolarity, hypotension, tachycardia, and risk for myocardial ischemia are the primary physiologic concerns in patients with DI. Preeclamptic patients may remain hypertensive despite significant intravascular fluid volume depletion due to DI.

Central DI is treated with desmopressin (DDAVP), which can be given intranasally. Desmopressin is resistant to vasopressinase, is not uterotonic, and appears safe for the fetus and nursing infant.[49,50] Nephrogenic DI does not respond to DDAVP and is treated with the oral hypoglycemic, chlorpropamide. In all cases, adequate fluid resuscitation should be confirmed prior to induction of regional anesthesia or GA. Central intravascular monitoring may be helpful in evaluating volume status.[51] Plasma electrolytes and osmolarity should be evaluated, and a urinary bladder catheter is recommended to monitor urine output. Hypotonic fluids may be indicated in cases of extreme hyperosmolarity when the oral intake of free water is restricted. With careful attention to volume status, electrolytes, and osmolarity, either general or regional anesthesia may be safely administered. Epidural anesthesia for C/S in a woman with gestational DI and severe hypernatremia has been described.[52]

The syndrome of inappropriate antidiuretic hormone secretion

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is most commonly reported in older, critically ill, and postoperative patients with inadequately treated pain. One case report describes a 32-year-old woman who developed SIADH on day five postpartum with symptoms of fatigue, weakness, dizziness, and nausea.[53] Other possible symptoms include weight gain, lethargy, confusion, seizure, and coma. Electrolyte testing demonstrates a serum sodium (Na^+) level < 130 mEq/l and serum osmolality < 270 mEq/l. Therapy includes pain management and fluid restriction to < 800 ml per day.

Panhypopituitarism

There are three major causes of panhypopituitarism in the peripartum period: iatrogenic, lymphocytic, and hemorrhagic. In addition, diabetic parturients with spontaneous pituitary necrosis may present with a midline headache, vomiting, and decreased insulin requirements. If unrecognized, the condition may result in fetal and maternal death.

Panhypopituitarism introduces significant perinatal risk even if managed appropriately. A review of eighteen pregnancies in nine women with panhypopituitarism found a high rate of pregnancy complications despite pituitary replacement therapy.[54] There were eleven (61%) live births, five (28%) first trimester abortions, and two (11%) second trimester intrauterine fetal deaths. There were no survivors from four sets of twins. Ten of the eleven live births were delivered by C/S, and 50% of those were small for gestational age.

Lymphocytic hypophysitis Lymphocytic hypophysitis is a rare autoimmune condition that most commonly presents in pregnancy or the postpartum period.[55] Lymphocytes and plasma cells infiltrate the anterior pituitary or the pituitary stalk, leading to pituitary enlargement followed by atrophy and fibrosis. In its most serious form, lymphocytic hypophysitis may lead to inadequate corticotropin release with potential for adrenal insufficiency, cardiovascular collapse, and death in the peripartum period. Other presentations include headache or visual changes due to an enlarging pituitary mass, or symptoms of specific hormonal deficits of thyrotropin, antidiuretic hormone, or gonadotropins. Lymphocytic hypophysitis can be associated with postpartum thyroiditis. Glucocorticoids are used to suppress the inflammatory response and protect remaining pituitary tissue. Steroids are important in cases of corticotropin deficiency and mass-related visual field deficits. Replacement doses of thyroxine, vasopressin, and gonadotropins may be necessary depending on symptoms and hormonal levels. Definitive diagnosis is by transsphenoidal biopsy.

Sheehan syndrome Sheehan syndrome occurs as a result of ischemic pituitary necrosis due to severe postpartum hemorrhage. It is seen rarely without massive hemorrhage. Improvements in obstetric care and blood-bank facilities have been associated with a marked reduction in the incidence of Sheehan syndrome in developed countries.[56] The presentation may include symptoms of DI, hypoadrenalism, hypothyroidism, hypoprolactinemia, and hypogonadism. Symptoms may develop as late as ten years following the initial obstetric event. Magnetic resonance imaging is useful to look for an empty sella tursica; however, an endocrinologic work-up is necessary to identify specific hormonal deficits. Although amenorrhea and infertility are common, spontaneous pregnancy may be possible if gonadal hormones are preserved. In such cases, appropriate thyroid and corticosteroid replacement are essential for maternal and fetal well-being.[57]

Anesthetic considerations for women with panhypopituitarism

In the stable patient, a diagnostic evaluation under the guidance of an endocrinologist will identify specific hormonal deficits and replacement goals. In unstable patients, it may be necessary to treat immediately with hydrocortisone, thyroxine, and fluid resuscitation with careful monitoring of intravascular volume and electrolytes. Patients on corticosteroids will require supplementation during labor and delivery (hydrocortisone 100 mg every eight hours). Regional and general anesthesia are safe provided there is adequate volume and hormonal replacement.

Adrenal

Pheochromocytoma

Pheochromocytoma is rare during pregnancy, but can be life threatening when it occurs. Symptomatic pheochromocytoma has an estimated prevalence of 20 per million pregnancies.[58]

Multiple endocrine neoplasia and neuroectodermal syndromes

Pheochromocytoma is less rare among women with multiple endocrine neoplasia (MEN) or neuroectodermal syndromes (see Table 16.7). Pheochromocytoma develops in 50% of patients with MEN 2A and 2B, in 25% of patients with von Hippel-Lindau syndrome (VHL), and in 5% of patients with neurofibromatosis.[59] Patients with familial pheochromocytoma are typically younger at diagnosis (32 versus 46 years), and are more likely to develop multifocal disease (55% versus 8%), and malignancy (11% versus 0%).[60] In one series of 82 patients with pheochromocytoma, 23% were carriers of familial disorders, so all patients with pheochromocytoma should be screened for associated genetic disorders.[60] Genetic testing is becoming available with specific mutations identified in the RET gene (seen with some forms of MEN 2), the VHL tumor-suppressor gene, the NF 1 gene (neurofibromatosis type I), and various succinate dehydrogenase subunits (pheochromocytoma-paraganglioma syndromes).[59] Patients and family members who test positive for one of these oncogene mutations may be candidates for prophylactic therapy. For example, in families with MEN 2 A, the RET mutation identifies children at risk for medullary thyroid cancer who will benefit from prophylactic total thyroidectomy.[61]

Maternal and fetal outcomes of pheochromocytoma

Historically, maternal and fetal mortality rates were 58% and 61% respectively.[62] The most common causes of maternal death were cardiovascular collapse, cardiac arrest, dysrhythmia, and intracerebral hemorrhage. Uteroplacental insufficiency leads to spontaneous abortion, IUGR, fetal hypoxia, and intrauterine fetal death. More recently, antenatal diagnosis and medical management of pheochromocytoma have improved outcomes. When antenatal diagnosis and medical management with alpha-adrenergic blockade are successful, maternal mortality may be reduced to zero and fetal mortality to 15% to 20%.[63,64] Nevertheless, maternal and neonatal deaths continue to occur,[65] with two maternal deaths attributed to pheochromocytoma in *The Sixth Report of the Confidential Enquiries into Maternal Death in the United Kingdom 2000–2002*.[66]

Clinical features

Prenatal diagnosis is the most important step in minimizing maternal and perinatal mortality. In the setting of pregnancy, the diagnosis can be missed because symptoms are often attributed to severe preeclampsia. Hypertension is the most common sign of pheochromocytoma, occurring in 98% of cases,[64] but episodes of hypertension may be either chronic or paroxysmal and transient. A multigravid woman with severe hypertension and no previous history of preeclampsia should prompt investigation for pheochromocytoma. In addition, glycosuria in the presence of a presumptive diagnosis of preeclampsia should point towards pheochromocytoma.[66]

Table 16.7 Syndromes associated with pheochromocytoma

Multiple endocrine neoplasia type 2A (Wermer syndrome)
Pancreatic B-cell islet adenoma
Pheochromocytoma
Medullary thyroid carcinoma
Carcinoid syndrome
Adrenal cortical adenoma
Multiple endocrine neoplasia type 2B (Sipple syndrome)
Mucocutaneous neuroma
Pheochromocytoma
Medullary thyroid carcinoma
Ganglioneuromas of visceral anatomic plexuses
Von Hippel-Lindau syndrome
Ataxia telangiectasia syndrome
Neurofibromatosis (von Recklinghausen syndrome)
Tuberous sclerosis
Sturge-Weber syndrome

If hypertension is paroxysmal, the patient may present with symptoms other than hypertension, including episodic headaches, pallor, palpitations, excessive sweating, spells of anxiety, tremor, fatigue, glucose intolerance, or dizziness due to orthostatic hypotension.[67] Finally, myocardial injury is a well-recognized complication of pheochromocytoma. Case reports have described women who presented with pulmonary edema and acute cardiac failure where peripartum cardiomyopathy, myocardial ischemia, or pulmonary embolus were considered before pheochromocytoma was diagnosed.[68,69,70] Cardiogenic shock requiring pressor support may develop following massive catecholamine release followed by catecholamine failure.[70] Other medical conditions that mimic pheochromocytoma include abdominal catastrophe, cerebral hemorrhage, epilepsy, eclamptic seizure,[71] cocaine or other sympathomimetic drug abuse, sepsis, MH, acute adrenal insufficiency, and thyrotoxicosis.[72] Nephrolithiasis may develop as a result of dehydration.

Because pheochromocytomas secrete heterogeneous patterns of catecholamines and catecholamine metabolites, no single biochemical analysis is perfectly accurate. The availability of laboratory testing varies by center, and the appropriate testing strategy varies based on family history and patient presentation. Therefore, consultation with a clinical pathologist is recommended prior to ordering diagnostic tests for pheochromocytoma. However, the combination of resting plasma catecholamines (norepinephrine and epinephrine) > 2000 pg/ml and urinary metanephrines (normetanephrine and metanephrine) > 1.8 mg in a 24-hour urine collection has a diagnostic accuracy of 98% for both sporadic and hereditary pheochromocytoma.[73] An alternative screening strategy is to measure fractionated plasma metanephrines only, which have a sensitivity of 97% and a specificity of 96% among those with a familial endocrine syndrome. For the general population, sensitivity is also high (99%), but specificity is only 82%, so a positive test should be followed up by more

complete testing.[74] For women with indeterminate biochemical results, a provocative test with glucagon or a suppression test with clonidine may help to distinguish patients with pheochromocytoma from those patients with essential hypertension or preeclampsia. However, each has the potential of inducing hemodynamic instability, and their use in pregnancy has been questioned.

Once the diagnosis is confirmed biochemically, radiological evaluation may be used to locate the tumor. Magnetic resonance imaging, CT and ^{123}Iodinated metaiodobenzylguanidine (^{123}I-MIBG) scans all have excellent sensitivity (95–100%), but MRI avoids ionizing radiation.[73] Ultrasound is a less sensitive alternative. Although most tumors are located in the adrenal medulla, approximately 10% can be found in the sympathetic ganglia located along the superior and inferior paraaortic areas, the bladder, thorax, head, neck, or pelvis.

Finally, if cardiomyopathy or CHF is suspected, echocardiography will define the extent of any cardiac dysfunction.

Table 16.8 Criteria for optimal preoperative preparation in pheochromocytoma

No BP higher than 160/90 mmHg in the 24 hours prior to surgery
Orthostatic hypotension should be present, but not less than 80/55 mmHg
The electrocardiograph should be free of ST-T segment changes
Premature ventricular contractions should be no more frequent than once every 5 minutes
Hematocrit decreased by ~5%

Adapted from Roizen M. F., Schreider, B. D. & Hassan, S. Z. Anesthesia for patients with pheochromocytoma. *Anesthesiol. Clin. North Am.* 1987; **5**: 269–75.

Management

Initial management is directed at controlling the hemodynamic response to catecholamines. Phenoxybenzamine, a long-acting α-blocker, is given orally (10 mg twice daily and increased by 10 mg/day until symptoms are controlled). Prazosin (1.5–2.5 mg q 6 h) or doxasocin (2–16 mg/day) are equally effective, and may have fewer side effects than phenoxybenzamine.[75,76] Labetalol may be added if tachycardia persists, but should not be given until α-blockade is established. Calcium channel blockers have also been used.

Once hemodynamic control is achieved, management varies by gestational age. Before 24 weeks' gestation, patients may have surgical resection of the pheochromocytoma through an open or laparoscopic approach.[77] After 24 weeks' gestation, patients are typically managed medically with phenoxybenzamine or another α-adrenergic antagonist until the fetus matures, at which time, open surgical resection may be combined with C/S. One case described the conservative management of pheochromocytoma from 14 to 35 weeks' gestation, with delivery by C/S. Three weeks later, tumor removal and total hysterectomy were performed.[78]

Plasma catecholamines are largely metabolized by placental catechol-O-methyl transferase and monoamine oxidase, with minimal transfer to the fetus.[79] In contrast, phenoxybenzamine crosses the placenta and appears to accumulate in the fetus. The fetal to maternal plasma phenoxybenzamine ratio has been measured at between 1.13:1 and 1.6:1.[80] Neonates exposed to long-term phenoxybenzamine may experience hypotension and respiratory distress in the first few days of life.[81]

Obstetric and anesthetic considerations

The preferred mode of delivery is C/S because uterine contractions and the maternal Valsalva maneuver may precipitate catecholamine release. However, there are case reports of uneventful vaginal deliveries among women with pheochromocytoma.[67,82] In one case, dense epidural anesthesia, minimal maternal pushing, vacuum-assisted delivery, manual delivery of the placenta, and ongoing hemodynamic monitoring and management allowed for a relatively stable hemodynamic course throughout delivery.[67]

The pregnant woman with an unresected pheochromocytoma is usually scheduled for a planned C/S. Preoperative preparation with 10 to 14 days of phenoxybenzamine therapy may be needed to achieve adequate α-blockade. Concomitant oral hydration will help expand the intravascular volume.

Criteria for adequate preoperative preparation in the nonpregnant patient are listed in Table 16.8. In pregnancy, the BP goal of $<$ 160/90 mmHg may represent inadequate preparation, and a more appropriate goal may be 10–15 mmHg below this value. Furthermore, orthostatic hypotension may not be advisable because it may impair uteroplacental perfusion and contribute to oligohydramnios. The FHR pattern should be monitored regularly while increasing the dose of antihypertensive medication.[83]

Patients with pheochromocytoma accumulate norepinephrine in their nerve terminals, and develop an exaggerated sympathetic response when stress and pain stimulate norepinephrine release. Therefore, attention to anxiolysis and analgesia is important. Preoperative sedation with a low dose of benzodiazepine reduces maternal anxiety and activation of the sympathetic nervous system. Intraoperative analgesia with a sufentanil infusion helps to control the physiologic response to pain.[84] Alternatively, regional anesthesia with an epidural catheter may control the exaggerated physiologic response to pain.

Both epidural anesthesia and GA are appropriate as long as care is taken to monitor and treat hemodynamic lability. Monitors include ECG, pulse oximetry, urinary bladder catheter, and arterial line. A second, large-bore peripheral i.v. cannula (14- or 16-gauge) is established to allow for rapid infusion of warmed crystalloid and colloid fluids intraoperatively. It may be prudent to place a central access sheath preoperatively, in case catecholamine-induced cardiomyopathy becomes apparent intraoperatively.

When GA is used, care must be taken to minimize the hemodynamic effects of intubation. Alfentanil (20–30 μg/kg) or fentanyl (2–3 μg/kg) and lidocaine (1–2 mg/kg) will reduce the incidence of ventricular dysrhythmias and prevent or attenuate the pressor response to endotracheal intubation. These drugs are followed immediately by induction with 4 mg/kg sodium thiopental or

0.3 mg/kg etomidate with 1.5 mg/kg succinylcholine. Rocuronium is preferred to succinylcholine if the tumor is embedded in skeletal muscle. Controlled ventilation with a mixture of nitrous oxide, oxygen, and isoflurane is acceptable for maintenance of GA. Drugs that release histamine, such as atracurium and morphine, are avoided, because histamine stimulates catecholamine release from chromaffin granules. Droperidol and metoclopramide should also be avoided as they may block inhibitory dopaminergic input to chromaffin cells.

Regional anesthesia with a lumbar epidural catheter has been used successfully for C/S and pheochromocytoma resection. In the presence of sympathetic blockade with epidural anesthesia, postsynaptic receptors still respond to the direct effects of catecholamines. Epinephrine should be removed from the test dose solution. Possible problems with this technique include hypotension following tumor vein ligation, and inadequate anesthesia if high abdominal exploration is required. An alternative anesthetic strategy is to use lumbar epidural anesthesia for the C/S followed by GA for the pheochromocytoma resection.[83] With either a regional or a GA technique, periods of paroxysmal tachycardia and hypertension should be expected before tumor resection, and profound hypotension can occur after the tumor is removed. Therefore, short-acting vasoactive infusions should be prepared for intraoperative hemodynamic management.

Sodium nitroprusside (SNP, 50 mg in 500 ml of 5% dextrose solution) can be infused to control BP intraoperatively (1 μg/kg/min). If the surgery includes removal of the pheochromocytoma, SNP should be terminated when the adrenal vein is clamped. Typically, recovery from the SNP infusion occurs within two minutes, thus preventing a rapid fall in BP once the tumor is removed. Fetal cyanide toxicity can become a problem if higher doses are used or maternal tachyphylaxis develops.

Magnesium sulfate (4 g i.v. loading dose, 1 g/h i.v. infusion, 2 g i.v. bolus p.r.n.) helps maintain cardiovascular stability during pheochromocytoma resection.[85] Magnesium sulfate has a direct vasodilator effect, reduces the sensitivity of the alpha-adrenergic receptors to catecholamines, and inhibits release of catecholamines from the adrenal medulla and peripheral adrenergic nerve terminals. Magnesium has been used to treat the symptoms associated with pheochromocytoma crises.[86] Magnesium has the additional benefit of being familiar to obstetric care providers.[87] If magnesium is used, blood levels should be checked and neuromuscular function carefully monitored as recovery may be impaired.

Other useful vasoactive medications include: phentolamine IV bolus (1–5 mg), nitroprusside IV bolus (1–2 μg/kg), esmolol, labetalol, and propranolol. Following resection, hypotension unresponsive to volume expansion with crystalloids or blood may be treated with an infusion of epinephrine, norepinephrine, or phenylephrine. Avoid using indirect sympathomimetics such as ephedrine.

Addison disease

Addison disease, or primary adrenal insufficiency, results in glucocorticoid and mineralocorticoid deficiency.[88] Patients with this disorder excrete excessive amounts of Na^+ in the urine but retain K^+, leading to hyponatremia and hyperkalemia. Adrenal insufficiency may occur as a result of pituitary or adrenal failure or destruction.

Primary adrenal insufficiency in the perinatal period may result from intrapartum hemorrhage, traumatic breech delivery, or fulminant sepsis.[89] Autoimmune adrenal insufficiency occurs at a rate of 2–3 in 100 000 as an isolated abnormality or as a part of an autoimmune polyglandular deficiency syndrome (types I and II). In type II, women aged 20 to 40 years have chronic immune thyroiditis and insulin-dependent diabetes mellitus.[90,91]

Other patient scenarios that may lead to mineralocorticoid insufficiency include prolonged administration of corticosteroids, congenital 21-hydroxylase deficiency,[92] and acquired immunodeficiency syndrome.[93] The antifungal drug ketoconazole may cause adrenal insufficiency because it inhibits mitochondrial cytochrome P450 enzymes such as cholesterol desmolase, 11 ß-hydroxylase, and aldosterone synthase.

Clinical features

With Addison disease, chronic primary adrenal insufficiency presents with an insidious history of malaise, anorexia, diarrhea, weight loss, joint and back pain. The cutaneous manifestations include darkening of the skin especially in sun-exposed areas and hyperpigmentation of the palmar creases, frictional surfaces, recent scars, genital skin, and oral mucosa.[88] Hyponatremia, hyperkalemia, and volume depletion typify aldosterone insufficiency. Because nausea, vomiting, fatigue, weakness, and hyperpigmentation are common symptoms of pregnancy, the diagnosis of adrenal insufficiency may be difficult. Clinical and laboratory features of adrenal insufficiency indicate deficiencies in cortisol and aldosterone. Plasma cortisol levels and cortisol-binding globulin levels are increased during normal pregnancy, but patients with Addison disease fail to show the expected rise in cortisol following adrenocorticotrophic hormone (ACTH) stimulation.

Maternal and fetal effects

Historically, Addison disease was associated with a high rate of maternal mortality but today, with adequate steroid replacement, pregnancy is associated with minimal risk.[94,95] Overall prognosis for the fetus and newborn is good, although there are reports of oligohydramnios, IUGR, and fetal distress.[96]

Management

Standard doses of glucocorticoids (hydrocortisone 20–30 mg/day) and mineralocorticoids (fludrocortisone 0.05–0.10 mg/day) are used during pregnancy. Most women tolerate labor and vaginal delivery well, but the potential for Addisonian crisis must be recognized. Fluid balance, glucose, and electrolyte levels should be optimized, and stress-dose steroids considered, particularly in cases of operative delivery.

Anesthetic implications

Current techniques of epidural analgesia or GA may be used when appropriate. Certain modifications are recommended for GA. Administration of incremental or low doses of anesthetic agents

is recommended to avoid the risk of drug-induced myocardial depression. Etomidate should be avoided because of the potential transient inhibition of cortisol synthesis. A peripheral nerve stimulator allows monitoring of neuromuscular blockade and titration of neuromuscular blocking agents, because skeletal muscle weakness is a typical feature of the disease. In cases of emergency surgery, hydrocortisone 100 mg may be administered every 6 hours for 24 hours. Invasive hemodynamic monitoring has been used to guide volume replacement. It is important to remember the potential for Addisonian crisis, hypotension, and circulatory collapse.

Addisonian crisis Addisonian crisis is a life-threatening condition that may be precipitated by the stress of labor and delivery, infection, or surgery. It may occur at any time during the peripartum period. Common presenting symptoms include abdominal pain, nausea, vomiting, and shock, which can be confused with an acute surgical emergency within the abdomen.

Circulatory collapse in Addisonian crisis has several possible mechanisms: loss of an enhanced response to catecholamines linked to steroids, altered receptor affinity, increased catecholamine metabolism, increased calcium (Ca^{2+}) uptake and altered electrolyte milieu, loss of cardiac glycogen, and decreased adenosine triphosphatase activity. In addition, reversible cardiomyopathy has been described in a patient with Addison disease.[97]

It is important to remain alert to this possibility in the undiagnosed patient with Addison disease. Therapy includes a bolus of 100 mg hydrocortisone followed by 300–400 mg of i.v. hydrocortisone infused over 24 hours.

Pseudohypoaldosteronism

Pseudohypoaldosteronism (PHA) type I is a class of genetic disorders characterized by elevated serum levels of aldosterone and aldosterone resistance. The autosomal recessive form is more severe. Infants typically present in the first two weeks of life with weakness, failure to thrive, hyponatremia, hyperkalemia, and metabolic acidosis, and require sodium chloride and K^+ binding resins throughout life to maintain electrolyte homeostasis.[98] The autosomal recessive form is caused by a loss-of-function mutation in the gene encoding the endothelial Na^+ channel, the primary mediator of aldosterone-dependent Na^+ transport in the distal nephron, colon, sweat glands, and salivary glands. In addition to electrolyte derangements, patients suffer from pulmonary congestion, wheezing, and secondary pulmonary infections. Autosomal dominant PHA type I is caused by mutations in the gene that encodes the mineralocorticoid receptor. Sodium chloride and K^+ binding resins may be necessary in infancy, but symptoms subside in childhood. Adult survivors continue to show marked elevations in aldosterone, but require no therapy, maintain normal electrolytes and BP, and have normal pulmonary function.[99] Pseudohypoaldosteronism type II (Gordon syndrome) is an autosomal dominant disorder that causes hypertension and hyperkalemia in the presence of a normal glomerular filtration rate (GFR), and serum aldosterone levels remain low or normal.[98] Cyclosporin, tacrolimus, and other calcineurin inhibitors may also cause aldosterone resistance mediated by a reduction in mineralocorticoid receptor expression.[98]

There are no reports of this condition in pregnancy.

Cushing syndrome

Cushing syndrome is produced by any condition associated with excessive cortisol production. Cushing disease is the term used when a pituitary tumor produces excessive amounts of ACTH. Pregnancy in patients with Cushing syndrome is rare because of infertility from anovulation, or from maternal complications such as hypertension, gestational diabetes, spontaneous abortion, and preeclampsia.[100] Cushing syndrome has been separated into two categories: (1) adrenal corticotropin hormone-dependent, which is associated with excessive plasma corticotropin concentrations, stimulating the adrenal cortex to produce markedly elevated cortisol levels; and (2) corticotropin-independent, which is associated with excessive production of cortisol by abnormal adrenocortical tissue that suppresses the secretion of both corticotropin-releasing hormone (CRH) and corticotrophin.[101] A 1990 literature review reported 58 pregnant women with Cushing syndrome. A benign adrenal adenoma was present in 40%, adrenal hyperplasia due to elevated ACTH of either pituitary or placental origin in 41%, and carcinoma in 10%. In four cases, the cause was undetermined, and one patient had ectopic ACTH from an ACTH-secreting pheochromocytoma.[102]

Clinical features

The typical features include weight gain, weakness, muscle atrophy, abdominal striae, easy bruising, edema, hyperpigmentation, thinning of the skin, pathologic fractures, and abnormal glucose tolerance. The diagnosis may be delayed or missed if signs and symptoms are attributed to normal pregnancy, preeclampsia, or diabetes mellitus.[100]

Biochemical diagnosis may be problematic because cortisol levels are elevated two- to three-fold during normal pregnancy, and much of this is protein bound. Pregnant women with Cushing syndrome may be identified because they typically lose the normal diurnal variation in cortisol levels and have increased urinary free cortisol.[103]

Patients with corticotropin-dependent Cushing syndrome show significant suppression of free cortisol and 17-hydroxycorticosteroid levels following a dexamethasone suppression test. In contrast, patients with corticotropin-independent Cushing syndrome fail to demonstrate suppression of baseline corticosteroid levels. Ultrasonography, MRI, or CT may be helpful in locating an adrenal or pituitary mass or bilateral adrenal hyperplasia.

Maternal and fetal effects

Cushing syndrome has significant morbidity and mortality for mother and fetus.[102] In a series of 67 pregnancies, 46% had preterm births, 12% spontaneous abortions, 7% stillbirths, and 34% term births. Other complications include IUGR, fetal hypertrophic cardiomyopathy,[104] and neonatal adrenal insufficiency. Maternal

complications include hypertension (65–87%), glucose intolerance (32–61%), CHF (11%), impaired wound healing (8–40%), pulmonary embolism, and maternal death (4.5%).[102,105] Other complications of Cushing syndrome in pregnancy include HELLP syndrome, preeclampsia, and multiple pathologic fractures.[106]

Management

Management during pregnancy may include unilateral or bilateral adrenalectomy, pituitary irradiation, pituitary adenectomy, or medical therapy with metyrapone or cyproheptadine. These interventions are associated with fewer premature births and stillbirths compared with supportive therapy alone.[105] Hence, surgery is the definitive and preferred treatment for women with severe symptoms. Surgery was traditionally performed at the end of the first or beginning of the second trimester, but there now are reports of laparoscopic and open adrenalectomy in the second and third trimesters.[107,108] Transsphenoidal hypophysectomy has been used successfully in mid-pregnancy for a woman with Cushing disease.[109] This case was complicated by patient obesity requiring awake fiberoptic intubation, diabetes with decreasing postoperative insulin requirements, and hypertension.[109]

Women who are not surgical candidates, or whose diagnosis is made later in pregnancy may be treated with metyrapone,[110] the 5-HT antagonist cyproheptadine, or ketoconazole,[111] all of which inhibit cortisol secretion. Each medication crosses the placenta and may cause fetal adrenal suppression. The risk for teratogenicity is unclear based on current evidence. Medical treatment is continued until the fetus is mature, at which time early delivery may be chosen depending on maternal and fetal status.

Anesthetic implications

It is important to evaluate coagulation, cardiovascular function, plasma glucose and electrolyte levels, and acid-base parameters prior to inducing any form of anesthesia. The greatest hazard during labor and delivery is severe hypertension. Thus, BP should be monitored frequently and appropriate treatment initiated promptly. Control of BP with hydralazine or labetalol is recommended. Severe hypertension may be associated with cardiac failure, which necessitates invasive monitoring. Polyuria and diabetes mellitus are frequent complications of Cushing syndrome and should be treated appropriately. Other complications include fluid retention, hypokalemia, and alkalosis.

If regional anesthesia is planned, it may be technically difficult due to central obesity, muscle wasting, osteoporosis with the potential for vertebral body collapse, and thinning and bruising of the skin.[112] Coagulation abnormalities or psychiatric disturbances may preclude regional anesthesia. There may be an exaggerated hemodynamic response to vasopressors, endogenous catecholamines, or sympathectomy. Hypotension should be avoided by careful positioning with left uterine tilt to avoid aortocaval compression, adequate fluid administration, and incremental injection of local anesthetics.

Many of these women require operative delivery. Either regional anesthesia or GA is appropriate, with the recognition that hemodynamic lability may be significant. Intraoperatively, invasive hemodynamic monitoring can assist in the management of serious complications, such as cardiac failure. For GA, consider awake fiberoptic intubation because central obesity, a buffalo hump, increased fatty tissue of the neck and sternal areas, and delicate mucosa may all contribute to a difficult airway.[109,112] Muscle weakness may reduce the dose requirements for neuromuscular blocking agents, and a peripheral nerve stimulator is essential for GA with pharmacologic paralysis.

If severe hypertension is present on arrival in the operating room, hydralazine or labetalol is used and BP is reduced to a range of 140–150 mmHg systolic and 90–100 mmHg diastolic. Before induction of GA, a diastolic BP can be maintained at 90 to 100 mmHg using 50-μg boluses of nitroglycerin (50–200 μg). After cord clamping, intravenous opioids reduce the release of cortisol secondary to surgical stimuli.

Conn syndrome

In primary hyperaldosteronism (Conn syndrome), excess mineralocorticoid secretion produces diastolic hypertension, hypernatremia, hypokalemia, kaliuresis, and metabolic alkalosis. Symptoms include headache, fatigue, weakness, and muscle cramps. Primary hyperaldosteronism is rare in pregnancy, with 29 cases reported in the literature up to 2002.[113] Patients present with hypertension resistant to therapy, and may develop uteroplacental insufficiency resulting in premature delivery, placental abruption, IUGR, or intrauterine fetal demise. Of 27 women with completed pregnancies, 85% had hypertension ($>140/90$ mmHg), 52% had proteinuria, 44% delivered prematurely, and 7% experienced an intrauterine fetal death.[113] Other potential complications include CHF, aortic dissection, dysrhythmias secondary to hypokalemia, hyperglycemia, hypercoagulability with thromboembolism, and pathologic fractures. Most cases are due to an adrenal adenoma (75%), but bilateral adrenal hyperplasia or adrenal carcinoma are also possible.[114] Approximately 5% of cases are caused by familial glucocorticoid-responsive hyperaldosteronism.[115]

Antihypertensive therapy with methyldopa, ß-adrenergic blockade, or calcium channel blockade is used to control hypertension. Some patients respond to glucocorticoid supplementation. Spironolactone does not appear to be teratogenic, but does have feminizing effects. Enalapril is not recommended for use in pregnancy. Potassium therapy may be necessary to correct hypokalemia. If medical therapy fails, then laparoscopic adrenalectomy in the second trimester is preferred.

Anesthetic implications

Epidural analgesia or GA may be used safely as long as attention is paid to hemodynamic stability, volume status, glucose levels, and electrolytes. Consider invasive cardiovascular monitoring if CHF is suspected or intravascular volume status is unclear. Hypokalemia may lead to dysrhythmias and may potentiate the effects of neuromuscular blockade.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) includes a family of genetic disorders of steroidogenesis. The most common is

21-hydroxylase deficiency, resulting in impaired cortisol production. Mineralocorticoid production may be affected as well. In response to impaired synthesis of cortisol, the hypothalamus increases ACTH secretion and ACTH stimulates adrenal precursors that lead to excess androgen production. Virilization of the female fetus with CAH can be avoided by dexamethasone administration to the mother. Therapy is begun before week nine of gestation in a high-risk woman. Genetic testing with amniocentesis or chorionic villus sampling is completed to determine the fetal sex and the presence or absence of the genetic mutation. Steroid therapy is continued only for women carrying an affected female fetus.[116]

Women with CAH often have amenorrhea, but may become pregnant with adequate steroid therapy and pharmacologic induction of ovulation.[117] Steroid therapy should be continued throughout pregnancy for women carrying a female fetus, because androgens, if allowed to develop, may cross the placenta and virilize the fetus. On the other hand, excess exogenous steroid also may cross the placenta and suppress the fetal adrenals, leading to transient adrenocortical insufficiency in the neonate. Cesarean section rates may be as high as 50% in women with CAH because of abnormal maternal external genitalia or a small bony pelvis.[118] Women on dexamethasone therapy will need steroid supplementation during labor and delivery.

Parathyroid glands

The four parathyroid glands produce parathyroid hormone (PTH). Along with vitamin D and calcitonin, PTH regulates Ca^{2+} homeostasis. During pregnancy, PTH-related peptide (PTHrP) is released by the fetus and placenta. This hormone shares a common receptor with PTH, and regulates active transport of Ca^{2+} across the placenta, creating a relative fetal hypercalcemia. It is found also in uterine smooth muscle where it is thought to regulate myometrial tone and blood flow. High levels of PTHrP may overload local hormone metabolism, lead to systemic maternal hyperparathyroid activity, and suppress maternal PTH release.

Up to 30 g of Ca^{2+} are delivered across the placenta to the fetus during a normal pregnancy. Nevertheless, maternal ionized Ca^{2+} levels are normally homeostatically regulated and stable through pregnancy at 1.5–2.5 mEq/dl. This active, ionized form represents only 40% of total blood Ca^{2+}. On the other hand, close to 50% of circulating Ca^{2+} is bound to albumin, and total blood Ca^{2+} levels fall because plasma albumin falls. The remaining 10% of circulating Ca^{2+} is chelated and physiologically inactive.

Hyperparathyroidism

The overall incidence of hyperparathyroidism is 0.15%, but is rarely reported in pregnant women. Hyperparathyroidism in pregnancy may be underreported; the true incidence may approach that of the nonpregnant population. This contradiction is explained by three considerations. Firstly, hyperparathyroidism is associated with an increased rate of early pregnancy loss. Secondly, the physiology of Ca^{2+} metabolism in pregnancy tends to be protective, with increased Ca^{2+} excretion across the placenta and through the kidneys. Thirdly, up to 80% of women with hyperparathyroidism are asymptomatic or experience vague symptoms attributed to normal changes of pregnancy.

Table 16.9 Presenting symptoms of hypercalcemia

Cardiovascular	Hypertension
	Dysrhythmias
Neuropsychiatric	Depression
	Psychosis
	Seizures
	Obtundation
	Coma
Gastrointestinal	Peptic ulcer disease
	Hyperemesis gravidarum
	Constipation
	Anorexia
	Nausea/vomiting
	Pancreatitis
Urinary	Nephrolithiasis
	Nephrocalcinosis
	Polyuria
Neuromuscular	Weakness
Skeletal	Osteoporosis
	Pathologic fracture
Miscellaneous	Thirst
	Pruritus

Adapted from Nader, S. Other endocrine disorders of pregnancy. In Creasy, R.K., Resnik, R., Iams, J.D. (eds.), *Maternal–Fetal Medicine: Principles and Practice*, 5th edn. Philadelphia: Saunders, 2004: pp. 1083–107.

The majority of cases are caused by a single parathyroid adenoma (80%). Less common etiologies include parathyroid gland hyperplasia, multiple adenomas, and carcinoma, and secondary hyperparathyroidism. Women who rely on calcium carbonate antacids to control gastroesophageal reflux symptoms may present with exogenous hypercalcemia with normal or decreased PTH levels.[119,120]

Women with hyperparathyroidism present with a variety of symptoms (see Table 16.9), and the maternal complication rate may be as high as 67%.[121] Nephrolithiasis appears to be the most common complication seen in 20–36%, and is associated with an increased risk of urinary tract infections (10–20%).[122] Radiographically demonstrated bone disease is apparent in 13–19%. In 10% of cases, calcification blocks the pancreatic ducts and lead to pancreatitis.[123] Hypercalcemic crisis is rare but serious, and is seen in patients with serum Ca^{2+} levels greater than 13 g/dl. Patients experience vomiting, hypertension, generalized weakness, dehydration, or mental status changes. The syndrome may be mistaken for hyperemesis gravidarum or preeclampsia. The greatest risk may be in the postnatal period, after transplacental shunting of Ca^{2+} to the fetus has stopped. In asymptomatic women, the first sign of maternal hyperparathyroidism may be neonatal hypocalcemia and tetany within 48

hours postpartum.[124] Historically, the perinatal complication rate has been as high as 80%. However, with appropriate therapy and perinatal surveillance, the complication rate may be reduced by a factor of four.[125] Complications include IUGR, low birth weight, fetal loss, preterm delivery, and neonatal hypocalcemia with or without tetany or seizures. For the fetus exposed to maternal hypercalcemia, fetal parathyroid development may be impaired, leading to either temporary or permanent neonatal hypoparathyroidism.

Management

Asymptomatic patients and those with mild symptoms may be managed conservatively with oral hydration, oral phosphates, limitation of Ca^{2+} intake, and electrolyte and fetal surveillance.[126] Patients with life-threatening complications such as pancreatitis, mental status changes, dysrhythmias, or hypercalcemic crisis should be hospitalized and treated more aggressively. Therapy includes fetal surveillance, i.v. fluid resuscitation followed by i.v. furosemide, electrolyte and cardiac monitoring, and surgical consultation. Calcitonin (pregnancy category B), oral phosphates (pregnancy category C), and bisphosphonates (pregnancy category C) may be considered. If symptoms persist, parathyroidectomy has a 95% success rate, and is most safely completed during the second trimester for patients with a single adenoma.[127]

Anesthetic implications

Women with hyperparathyroidism may receive usual anesthetic care with either regional anesthesia or GA depending on the clinical circumstances. However, it is important to first measure both total and ionized serum Ca^{2+} levels and to assess volume status. In the presence of significant hypercalcemia, hydration with normal saline should be titrated to ensure adequate urinary output and to reduce the total Ca^{2+} level below 14 mg/dl. Hypovolemia and hypercalcemia may lead to hemodynamic instability and cardiac dysrhythmias. Perioperative monitoring of the EKG for prolonged PR interval, wide QRS complex, or a shortened QT interval may help identify physiologically significant hypercalcemia. Somnolence and muscle weakness increase the risk of aspiration and may decrease anesthetic dose requirements. Muscle weakness and electrolyte imbalance may also lead to unpredictable responses to succinylcholine, nondepolarizing muscle relaxants, and neuromuscular blockade reversal agents. Careful positioning is important, particularly in patients with osteoporosis at risk for pathologic fracture.[128]

Hypoparathyroidism

Hypoparathyroidism is rare during pregnancy. It is most commonly iatrogenic following thyroidectomy or parathyroidectomy. Other etiologies include genetic, hypomagnesemia, chronic renal failure, or autoimmune related dysfunction. Significant hypocalcemia is present when the total serum Ca^{2+} level is < 4.5 mg/dl or the ionized Ca^{2+} concentration is < 2.0 mEq/l. The differential diagnosis of hypocalcemia includes vitamin D deficiency, chelation following rapid blood transfusion, pancreatitis, and sepsis.

The clinical presentation of acute hypocalcemia includes inspiratory stridor, skeletal muscle irritability, laryngospasm, paresthesia, and seizures. Chronic hypocalcemia may lead to symptoms of fatigue, skeletal muscle cramping and weakness, lethargy, and personality changes. Signs of hypocalcemia include Chvostek sign (facial muscle spasm when the facial nerve is tapped) and Trousseau sign (carpopedal spasm when a BP cuff is inflated for three minutes). Cardiovascular consequences of hypocalcemia include hypotension, elevated LV pressure, myocardial dysfunction, cardiac dysrhythmia with prolongation of the QT interval, and CHF. Fetal consequences include prematurity, fetal loss, intracranial bleeding, fetal and neonatal hyperparathyroidism, fetal bone demineralization with fractures, neonatal respiratory distress syndrome, and IUGR.[129] Fetal death from complications of fractures may occur.

Management

Women with hypoparathyroidism should have regular electrolyte monitoring, including Ca^{2+}, magnesium, and phosphate levels. For patients with mild or asymptomatic hypocalcemia, a diet high in Ca^{2+} and low in phosphate may be combined with Ca^{2+} and vitamin D supplementation. Calcitrol, the physiologically active form of vitamin D, is used most often, and is titrated to maintain ionized serum Ca^{2+} concentrations between 2.0 and 2.2 mmEq/l.[129] Doses typically increase throughout pregnancy, and then fall rapidly postpartum, particularly in lactating women.[130] Thiazide diuretics and Na^{+} restriction may be helpful. Symptomatic or severe hypocalcemia (< 3.5 mg/dl) should be corrected with calcium gluconate (5–10 ml of a 10% solution) until signs of neuromuscular irritability or cardiovascular dysfunction subside.

Anesthetic implications

Anesthetic management should be directed at maintaining Ca^{2+} levels and minimizing the consequences of hypocalcemia. Calcium, phosphate and magnesium levels should be checked before any anesthetic procedure. Maternal hyperventilation and respiratory alkalosis will acutely exacerbate hypocalcemia, so regional anesthesia for labor and delivery may help to minimize shifts in Ca^{2+} concentrations. Either regional anesthesia or GA may be used for C/S. The EKG should be monitored for prolongation of the QT interval or cardiac dysrhythmias including 2:1 heart block. Calcium monitoring is particularly important if rapid transfusion of citrated blood becomes necessary. Hypocalcemia also may impair coagulation, and a review of coagulation parameters prior to regional anesthesia is prudent. Finally, extubation may be complicated by laryngospasm in patients with acute hypocalcemia.

Conclusions

Rare endocrine disorders are often a manifestation of a multisystem disorder, and may result from altered regulation of circulating hormone levels. Crises and emergencies typify the problems in diagnosis and management of rare and complex endocrine disorders. We recommend a coordinated team approach, with early consultation of the anesthesiologist, to facilitate medical management.

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17 BLOOD DISORDERS

M. Joanne Douglas and Penny Ballem

Background

Normal hematological indices during pregnancy

Multiple changes occur to the hematological system during pregnancy as outlined in Table 17.1.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15] It is essential that the clinician be familiar with these in order to determine what is normal and what is abnormal when reviewing laboratory results in the pregnant woman.

Hematological testing during pregnancy

A routine, complete blood count during early pregnancy (first trimester) is important to identify common, preexisting hematological disorders that may impact on the pregnancy. In the uncomplicated pregnancy, a repeat blood count in the third trimester is done to assess the hematocrit in preparation for delivery.

Coagulation screening is performed only:

- to investigate a significant bleeding history
- to follow factor levels in patients with established disorders
- during acute peripartum complications such as preeclampsia, massive hemorrhage or disseminated intravascular coagulation (DIC)
- to monitor anticoagulation therapy.

Screening assays include platelets, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen (see Table 17.2). The subjective nature of the bleeding time as a measure of platelet function and its established lack of sensitivity and specificity[18,19] as a predictor of clinical bleeding, has precluded its usefulness.

Currently, several centers use thromboelastography (TEG) to detect the risk of clinical bleeding;[20] however, the sensitivity and specificity of this test remain unproven.[21] Another point of care instrument, the platelet function analyzer (PFA-100®), is thought to represent an "in vitro" bleeding time. Although small studies have been done in obstetric patients, the evidence at present is insufficient to recommend its routine use in predicting platelet function and the risk of an epidural hematoma.[21] Thus, the ability of any test to predict the risk of bleeding into the epidural space during regional anesthesia remains unknown.

Transfusion during pregnancy

The indications for transfusion of blood products during pregnancy are relatively few. In most instances, the need for blood products arises in preparation for delivery in patients with preexisting disorders or in response to an acute peripartum complication such as acute abruption with DIC, severe preeclampsia, or postpartum hemorrhage (PPH). Careful counseling of the patient should be undertaken, even under emergent conditions, to alert them to the risks of blood products. In patients considered at high risk of hemorrhage, techniques used to attempt to decrease the need for homologous transfusion include autologous donation,[22] and, at the time of operative delivery, acute hemodilution.[23]

Significant advances have been made in the inactivation of viruses in the manufacture of fractionated blood products (e.g. clotting factor preparations); however, it is critical that we continue to balance benefit of transfusion with risk of viral transmission. Recombinant gene technology has enabled the development of some products, such as specific coagulation factors. For the most part, the cost of these preparations is still prohibitive and we still remain dependent on plasma-derived products. However, recombinant activated factor VII (rVIIa) is being used increasingly to treat massive hemorrhage in the obstetric patient, as well as for specific factor deficiencies or acquired factor inhibitors (see below).[24,25,26]

Apheresis

Apheresis involves the separation of blood into its various components and is a technique used during pregnancy to treat certain conditions (e.g. myasthenia gravis, thrombotic thrombocytopenic pupura), through the removal of a causative antibody. A complete review on this topic discussed the risks and potential benefits and outlined the reports where it has been used in pregnancy.[27]

Red cell abnormalities and anemias

Anemia occurs commonly during pregnancy, frequently due to hemodilution, (physiologic anemia of pregnancy) or improper nutrition, such as inadequate intake of iron or folate. However, the broad spectrum of hemoglobinopathies, thalassemic syndromes, hemolytic anemias, and anemias related to primary bone marrow disorders can all occur in pregnancy. Furthermore, there is an increasing number of pregnant women with chronic disorders, such as renal failure, solid organ transplants, and rheumatologic conditions, which can be associated with anemias related to impaired erythropoiesis or drugs. The management of these patients relates to the potential effect

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Table 17.1 Hematological changes of normal pregnancy[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15]

Parameter	Direction of change	Time of peak or nadir
Blood volume	Increase (45–55%)	34–36 weeks
RBC mass	Increase (15–20%)	Term
Ferritin	Decrease	28–32 weeks
MCV	Increase	24–28 weeks
WBCs	Mild–moderate increase (25%)	Term
Platelet count	Same or decrease	32–36 weeks (nadir)
Factors VII, VIII, X, XII	Increase	
Fibrinogen	Increase	Term
Factor IX	Unchanged	
Factor XI	Decrease (62%)	Term
Protein C	Unchanged	
Protein S	Decrease (40–50%)	12 weeks
ATIII	Unchanged	

RBC = red blood cell; WBC = white blood cell; MCV = mean cell volume; AT III = antithrombin III

Table 17.2 Common coagulation studies and findings in factor deficiencies[16,17]

Factor deficiency	PT	aPTT	TT
I	prolonged[a]	prolonged[a]	prolonged
II	prolonged	may be prolonged	normal
V	prolonged	may be prolonged	normal
VII	prolonged	normal	normal
VIII	normal	prolonged	normal
VWF	normal	prolonged	normal
IX	normal	prolonged	normal
X	prolonged	prolonged	normal
XI	normal	usually prolonged	normal
XII	normal	prolonged	normal
XIII	normal	normal	normal

[a] Less sensitive than thrombin time
PT = prothrombin time; aPTT = activated partial thromboplastin time; TT = thrombin time

of the anemia on maternal and fetal well-being. An understanding of the pathophysiology of the anemia, inheritance patterns, and other mechanisms of involvement of the fetus is essential. Transfusion of red blood cells (RBCs) is only one potential intervention and other therapeutic maneuvers should be weighed against the risks associated with transfusion. In most patients, particularly those with long-standing anemia, there is good physiologic compensation in the mother and expectant management is appropriate. The use of erythropoietin in pregnancy is still controversial, with numerous case reports of its use in Jehovah's Witness parturients at high risk of hemorrhage or in parturients on dialysis. Maternal hypertension has been seen in women on erythropoietin.[28]

Anesthetic considerations for the management of parturients with anemia

Patients with compensated anemia tolerate anesthesia well. The choice of anesthetic technique and specific drugs are determined by the underlying disease. There is no clear threshold hemoglobin level below which transfusion is essential. In a well-compensated patient, with chronic iron deficiency for example, a cesarean section (C/S) can be undertaken safely with a hemoglobin below 8 g/dl. Unless there is evidence of ongoing hemolysis, active bleeding or severe symptomatology, compensated anemia should not be treated with transfusion. If transfusion is required then proper counseling of the patient should be undertaken with regard to the risks. Supplemental oxygen should be administered to women with a hemoglobin level less than 8 g/dl although 7 g/dl is the level when compensatory changes to cardiac output occur.

Regional techniques are not contraindicated unless there is a concomitant hemostatic defect due to dysfunctional platelets (uremia) or thrombocytopenia (such as aplastic anemia). The temperature of the environment should be controlled for patients with temperature-sensitive hemolysis. In patients with combined cytopenias (thrombocytopenia and neutropenia), consideration should be given to appropriate interventions such as antibiotics, or transfusion of specific products, such as platelets.

Thalassemias and hemoglobinopathies

Inherited abnormalities of hemoglobin synthesis (thalassemias) or structure (hemoglobinopathies) are important from the perspective of the fetus and mother.[29] Inherited abnormalities of hemoglobin structure or synthesis may produce asymptomatic maternal anemia or lead to severe complications with increased perinatal morbidity and mortality.[30] For practitioners caring for women with a hemoglobinopathy who are in the early stages of pregnancy, it is important to discuss their need or desire for prenatal diagnosis.[30] In patients with ongoing chronic extravascular hemolysis and ineffective erythropoiesis, iron overload is an important and usually avoidable complication. Thus, iron supplementation in pregnancy should be withheld pending review of the serum ferritin. Supplemental folic acid is essential in all patients with these syndromes, due to the extra demands placed on the marrow in pregnancy.

Thalassemia

The thalassemia syndromes are a group of inherited disorders that lead to quantitative defects in the synthesis of globin chain subunits.[29] For example, there is deficient production of the alpha-globin chain in alpha-thalassemia and of the beta-globin chain in beta-thalassemia, the two most common thalassemias seen in North America. The majority of patients with thalassemia have a benign carrier state (heterozygous beta thalassemia and the 2 gene deletion of alpha thalassemia) and these usually present as a mild

anemia in early pregnancy. Most follow a similar pattern to their nonthalassemic counterparts, with the physiologic anemia of pregnancy causing a drop in hemoglobin, which is progressive until the middle of the last trimester. The nadir of the hemoglobin will be significantly below the normal range for pregnancy, but these patients usually compensate well for the degree of anemia.

The 3 gene deletion state of alpha thalassemia (hemoglobin H disease) is usually a mild to moderate hemolytic anemia in the nonpregnant state, associated with splenomegaly and chronic anemia. By the third trimester, some patients with this disorder may be symptomatic from anemia. Fetal well-being and growth should be followed carefully, and either evidence of compromise of the latter or significant symptoms in the mother may be an indication for transfusion.

There is limited experience with patients who have the most severe form (homozygous state) of β-thalassemia in pregnancy. Many have symptomatic hemosiderosis by the time they reach the childbearing years with associated delayed sexual development and cardiomyopathy. Fourteen pregnancies in nine patients with homozygous β-thalassemia are reported in the literature.[31] Obstetric management was complicated by severe anemia, chronic hypoxia, and myocardial hemosiderosis from iron overload. Cardiac dysrhythmias and congestive heart failure are common in this setting and are aggravated by the physiological changes of pregnancy. Fetal problems included fetal loss, preterm labor, and intrauterine growth restriction (IUGR). Another rare, reported complication in a pregnant woman with thalassemia is spinal cord compression by extramedullary hematopoiesis.[32] Treatment with blood transfusion resulted in a complete recovery. Bone marrow transplantation is being used to treat this disorder and there is one report of a successful pregnancy following this procedure.[29]

In a population-based study, pregnancy associated with thalassemia minor was uneventful, other than for a high rate of IUGR.[33]

Hemoglobinopathies[29]

The homozygous states for hemoglobin C (α_2/β_{c2}) and E (α_2/β_{e2}) are relatively benign conditions that may present clinically as chronic hemolysis. Such patients behave in pregnancy as any patient with chronic hemolytic anemia, with increased demand for the nutritional building blocks used for erythropoiesis. Individuals with these disorders are susceptible, although rarely, to a number of acute crises: megaloblastic crisis from inadequate folate supplementation, and aplastic and hypersplenic crises, which may follow acute viral illness. These patients may present with combined abnormalities particularly in association with the thalassemias. Some combinations are beneficial in terms of the severity of anemia (for instance, patients with beta-chain hemoglobinopathies generally do better than those with alpha-thalassemia trait) and others detrimental, with a more severe clinical course.

Anesthesia in the thalassemias and hemoglobinopathies

Anesthetic concerns relate to the underlying cardiac status in the setting of severe forms of thalassemia and, more commonly, to the degree of hemodynamic compensation with regard to the chronic anemia, its relative oxygen-carrying capacity, and its relationship to anesthesia. There is no specific contraindication to the use of a particular anesthetic technique. However, in the severely anemic patient, narcotic analgesia for labor is relatively contraindicated due to the increased risk of hypoxemia, and, if used, oxygen saturation should be monitored and oxygen supplementation provided, if required. There are risks and benefits to general and regional anesthesia for C/S. Careful attention must be paid to fluid balance.

There is one report of successful intraoperative blood salvage in a woman with placenta accreta and β-thalassemia intermedia who refused transfusion of blood products.[34]

Sickling syndromes

Of the clinical sickling disorders, Hb SS and Hb SC disease have the most impact in pregnancy. Anemia is common and, as there is an increased risk of infection and vaso-occlusive crises,[29,35,36] frequent assessment is required throughout pregnancy.[29,30] There is an increased incidence of IUGR due to vaso-occlusion of placental vessels.[29] In a cohort study of women with Hb SS disease there was an increase in early fetal loss.[37] The use of prophylactic red cell transfusion to maintain Hb A levels above 20% to minimize sickling is controversial due to the risk of transfusion transmitted infection.[29,38,39] Some recommend transfusion only in those patients who develop complications during pregnancy.[39] There is evidence to suggest that, in patients who receive transfusion, the use of leukodepleted red cells reduces febrile transfusion reactions and viral transmission but no data prove a particular benefit.[40] Maternal mortality in sickling disorders is generally due to septicemia, thromboembolism, or cardiac failure after a hemolytic crisis.[35] Chronic lung disease, secondary to obliteration of pulmonary arterioles and interstitial fibrosis, has been reported and may lead to pulmonary hypertension and right heart failure.[41]

Other sickling syndromes are milder with improved maternal and fetal outcome. Hb SD disease is rarer than Hb SS but maternal and fetal outcome is generally better. The combination of Hb S and Hb F does not generally produce clinical problems. Hb E when combined with Hb S produces mild disease. Sickle cell trait is the heterozygous form of sickle cell disease with a hemoglobin phenotype AS. It is benign with most patients being asymptomatic. However, such patients will still have increased demands for erythropoiesis in pregnancy and supplemental folic acid is essential.

Anesthesia and the sickling syndromes

Anesthetic management aims to prevent sickling (see Figure 17.1). As sickling tends to occur under conditions of stasis, hypothermia, acidosis, and hypoxemia, anesthetic management should attempt to avoid these.[42] Areas of anesthetic controversy in sickle cell disease include use of direct intra-arterial pressure monitoring in preeclamptic patients (stasis from a noninvasive blood pressure cuff vs. risk of vaso-occlusion), regional versus general anesthesia (generally accepted that regional is best although some suggest otherwise) and use of prophylactic blood transfusion (possible improved outcome vs. risk of disease).[42]

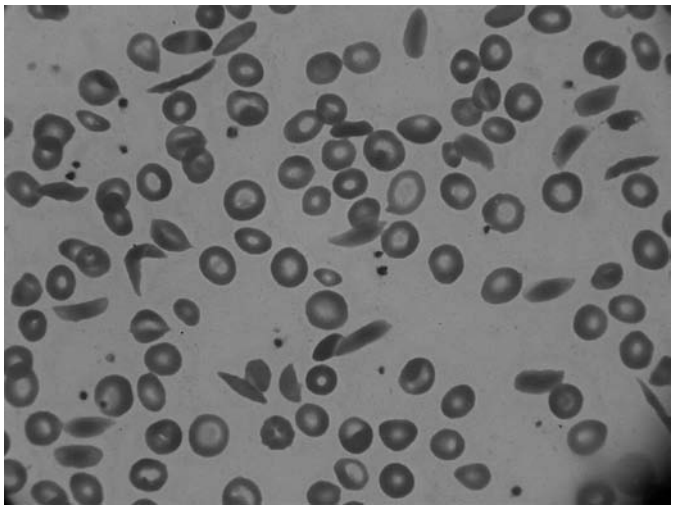

Figure 17.1 A typical peripheral blood smear from a patient with sickle cell disease demonstrating numerous sickle cells and a rare target cell. (See color plate section.)

Epidural analgesia has been used for labor analgesia as well as for control of the pain during sickle cell crisis.[43] There are two reports of a sickle cell crisis in previously asymptomatic parturients with sickle cell disease; one was attributed to induction of labor and the other to stress during labor. Both received neuraxial analgesia for the management of pain.[44,45] Shivering increases oxygen consumption and may be detrimental to the patient with sickle cell disease. Efforts should be made to limit it by using warm intravenous fluids and possibly forced air warming devices and by keeping the environmental temperature warm. Measurement of oxygen saturation during labor and delivery will guide the use of supplemental oxygen.

Regional and general anesthesia are acceptable for C/S,[46,47] although a review of surgery in sickle cell disease found that sickle cell disease-related postoperative complications were more frequent in Hb SS patients who received regional anesthesia.[48] The authors postulated that the results could have been affected by the fact that C/S is more commonly performed under regional anesthesia and might be associated with more complications than other surgery.

Principles of anesthetic management include maintenance of intravascular volume (crystalloid), supplemental oxygen to avoid sickling from hypoxia, avoidance of acidosis, adequate left uterine displacement, maintenance of normothermia, and prevention of peripheral venous stasis. The above principles apply to all patients with any capacity for sickling, including the heterozygous Hb S carrier state. In the more severe disorders, especially Hb SS, transfusion of warmed RBCs to maintain oxygen-carrying capacity and increase the blood content of Hb A, when appropriate, is the other parameter to be considered, although this is controversial.[42] Furthermore, as these patients are at risk of high output cardiac failure, some may require more invasive monitoring. Oxygen saturation monitoring should be continued during the postoperative period as hypoxia may occur.

Complications from anesthesia in patients with sickle cell trait are rare. There has been one case of an intraoperative death during C/S in a patient with sickle cell trait.[49] Death was attributed to severe, concealed aorto caval compression: such that once it was relieved a large volume of hypoxemic, acidotic blood was returned to the circulation causing cardiac arrest.[49] In another report, a parturient with Hb SS disease developed progressive neurologic symptoms post-C/S under spinal anesthesia. Initial symptoms were attributed to vasoocclusive pain crises. However, progression of symptoms suggested a pulmonary embolus, followed by bilateral motor and sensory deficits in a T_{11}-S_2 distribution. The woman received anticoagulation following a normal MRI scan and she made a full recovery.[50] There is one report of the use of an epidural colloid patch in a woman with Hb SS disease who developed a postdural puncture headache following spinal anesthesia. The authors were reluctant to do an epidural blood patch for theoretical safety concerns, including a local inflammatory reaction leading to activation of the coagulation cascade and a risk of a medullar vasoocclusive crisis.[51]

There are two case reports of pheochromocytoma associated with sickle cell disease.[46,52] In one case, the woman had a combined C/S and excision of the pheochromocytoma under general anesthesia.[46] Prior to that surgery she had an exchange transfusion to increase her levels of hemoglobin A. In the second case where a pheochromocytoma was suspected, the woman had a C/S under combined spinal–epidural anesthesia followed by removal of the pheochromocytoma five months later.[52]

Hemolytic anemias

Hemolytic anemias are classified as inherited or acquired. Of the inherited group the most common are secondary to:

- *membrane disorders* making the red cell less flexible in the microcirculation and, thus, susceptible to hemolysis
- *metabolic abnormalities*, which increase sensitivity to oxidant stress. Abnormal hemoglobins may make the RBC susceptible to hemolysis.

Acquired disorders causing RBC hemolysis fall into two main groups:

- those related to immune-mediated hemolysis
- those associated with mechanical hemolysis due to microangiopathy or other uncommon mechanical stresses (mechanical hemolysis related to artificial heart valves).

Hemolysis can occur in the intravascular space causing release of free hemoglobin with resulting hemoglobinuria and hemosiderinuria, or more commonly extravascularly in the reticuloendothelial (RE) system primarily of the liver and spleen. Common laboratory parameters of ongoing chronic hemolysis include a raised reticulocyte count, increased lactic dehydrogenase (LDH), increased unconjugated bilirubin, and, in specific disorders, morphologic abnormalities on the peripheral smear.

Inherited hemolytic disorders

Hereditary spherocytosis This autosomal dominant disorder has an incidence of 200–300 per million population and is the most common membrane disorder. The pathognomonic feature is the presence of spherocytes in peripheral blood associated with

increased osmotic fragility of red cells on special testing in the laboratory. As a result of increased destruction of the abnormal cells in the RE system, these patients commonly present with anemia, splenomegaly, and jaundice. Splenectomy is curative, but because of the usually mild nature of this disorder, many patients do not undergo splenectomy.[53] The diagnosis may be made during pregnancy,[54,55] and although there are reports of hemolytic crises during pregnancy most patients tolerate pregnancy well.[56,57] Routine supplementation with folic acid and, if indicated (following assessment of serum ferritin), iron is necessary in order to ensure effective erythopoiesis. In the rare event of severe anemia, splenectomy may be required. As anemia may worsen during episodes of infection (due to increased hemolysis and possibly suppressed hematopoiesis) these patients require frequent monitoring.

Other membrane abnormalities include hereditary elliptocytosis and hereditary stomatocytosis; neither of these are improved by splenectomy and most patients have a mild chronic hemolytic anemia, which is unaffected by pregnancy.

Red cell enzyme deficiencies The most common hereditary deficiencies are those of glucose-6-phosphate dehydrogenase and pyruvate kinase. Both of these enzyme deficiencies make the RBC susceptible to oxidant stress leading to an increased susceptibility to hemolysis. The degree of hemolysis varies, with more severe episodes often triggered by oxidant drugs including some antibiotics and nonopioid analgesics.

Acquired disorders of the RBC leading to hemolysis

Autoimmune hemolytic anemias These hemolytic anemias result from the development of warm (IgG) or cold (IgM) reactive red cell autoantibodies. These disorders can occur at all ages but are more common in adults, particularly women. Autoimmune hemolytic anemia is usually idiopathic but may occur secondary to drugs such as α-methyl dopa or in association with an underlying disease (about 25% of patients) such as systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel disease, or a lymphoproliferative disease (e.g. chronic lymphocytic leukemia, non-Hodgkin lymphoma).

Patients with IgG autoantibodies (warm, reactive) are more common and present with anemia, mild icterus, and splenomegaly. Laboratory findings include reticulocytosis, and the presence of spherocytes on the peripheral smear. If immune thrombocytopenia is present in conjunction with autoimmune hemolytic anemia the condition is known as Evan syndrome.[58] Patients with idiopathic, immune hemolytic anemia usually respond well to corticosteroid therapy at a 1 mg/kg dose of prednisone. IgG autoantibodies have the potential to cross the placenta and cause fetal anemia. Transfusion should be avoided unless the patient is very symptomatic or the fetus is compromised by severe maternal anemia. Cross matching of blood may be difficult due to the presence of other alloantibodies.

In patients with immune hemolysis due to cold-reactive antibodies (IgM), the pathophysiology of hemolysis is different, resulting largely from the fixation of complement on the red cell membrane with resultant hemolysis in the intravascular space. Thus, these patients may not have splenomegaly. They do not have spherocytes on a peripheral smear but show reticulocytosis, raised LDH and bilirubin, and increased hemosiderin in the urine. This condition is rare in pregnancy, and does not respond well to corticosteroids. Transfusion can be problematic and the use of a blood warmer and maintenance of a warm environment is critical. Since IgM antibodies do not cross the placenta, fetal involvement does not occur.

Pregnancy-induced hemolytic anemia This extremely rare condition presents as hemolytic anemia during the third trimester and remits spontaneously postpartum. The anemia is severe and may become life-threatening, such that some women require transfusion. Corticosteroids and intravenous immunoglobulin (IVIG) have been tried but without uniform success. To date no cause has been found and treatment is empirical.[59]

Miscellaneous causes of hemolysis

Hemolysis may occur in patients with normal RBCs, secondary to trauma from prosthetic heart valves or secondary to fibrin deposition in the microvasculature (microangiopathic anemia). In the former situation, chronic hemolysis during pregnancy will be associated with a raised LDH, possibly mild icterus, reticulocytosis, and hemosiderinuria with decreased plasma haptoglobin. Supplementation with folic acid and iron is usually necessary to allow the bone marrow to compensate for ongoing loss. Microangiopathic hemolytic anemia is associated with acute DIC, preeclampsia, or acute vasculititis and treatment of the underlying disorder is essential.

Abnormalities of the bone marrow

Bone marrow failure syndromes

Aplastic anemia

Aplastic anemia is a primary bone marrow disorder caused by hypocellularity of the marrow with resulting pancytopenia in the peripheral blood. The etiology of marrow hypoplasia is varied and aplastic anemia has been associated with exposure to radiation, organic solvents, various drugs, immune lesions and viral disease, particularly the hepatitis viruses. Other more unusual defects may involve only one cell line such as anemia due to RBC aplasia, or neutropenia due to white blood cell (WBC) aplasia. In the past, aplastic anemia was associated with a dismal prognosis but bone marrow transplantation from a matched sibling donor has a reported success rate of 90%. Supportive therapy is often required and immunosuppression is another treatment modality.[60] Blood counts in nonpregnant patients who respond to immunosuppression may never become completely normal, and these patients are at risk for relapse of aplasia or development of paroxysmal nocturnal hemoglobinuria (PNH), a myelodysplastic syndrome, or acute leukemia.[61]

Approximately 50% of cases of aplastic anemia are idiopathic in origin. There are sporadic case reports of refractory hypoplastic

anemia, which appear to be related to pregnancy and which regress postpartum.[62,63,64,65,66,67] However, the majority of women affected in pregnancy have become pregnant during the course of chronic aplastic anemia.[68] Due to increased plasma volume and the inability of bone marrow to respond it is common for peripheral cytopenia to worsen during pregnancy and to improve postpartum.

Pregnancy in women with aplastic anemia is considered high risk due to the high incidence of perinatal morbidity and mortality.[69,70] To date, there is conflicting evidence as to the effect that pregnancy has on aplasia and vice versa. Aplasia has been discovered during pregnancy and occasionally aplasia may completely resolve postpartum. One retrospective study describes pregnancy in 36 women who received immunosuppressive therapy for aplastic anemia.[61] Twenty-two pregnancies were uncomplicated, but seven women (19%) had a relapse of aplasia and three of these had remission of their disease while three more recovered after treatment. One who did not have a remission died. Complications were related to low platelet counts and PNH-associated aplastic anemia. Women who had a relapse during pregnancy or had progressive thrombocytopenia had an operative delivery. Anesthetic management is not discussed.[61]

The major risks of aplastic anemia during pregnancy are severe anemia, hemorrhage due to thrombocytopenia, and infection associated with neutropenia.[71] In the past, women with aplastic anemia were advised not to become pregnant or, if pregnancy occurred, to terminate the pregnancy. With transfusion support, particularly platelets, this may not be appropriate advice for those with mild to moderate disease.[68,72] However, some authors still debate this.[70] The best outcome from pregnancy is achieved with a multidisciplinary approach involving obstetricians, hematologists, and anesthesiologists.[73]

Congenital red cell aplasias

Primary red cell aplasia

Primary red cell aplasia (PRCA) is a rare disease associated with progressive anemia, marked reticulocytopenia, and almost complete absence of RBC precursors in the marrow. Production of WBCs and platelets is normal. The congenital form is known as Diamond-Blackfan syndrome or anemia and it usually presents in infancy (see below). Acquired PRCA has been associated with thymoma, chronic lymphocytic leukemia, renal failure, pregnancy, and various autoimmune disorders.[74,75]

Fanconi anemia

Fanconi anemia is a rare congenital RBC aplasia, which is inherited as an autosomal recessive trait. Characteristics are progressive bone marrow failure, skeletal defects, reduced fertility, and increased susceptibility to malignancy. There is a report of a pregnant woman with Fanconi anemia who received "washed" RBCs during pregnancy, was induced at term for preeclampsia, and delivered by C/S. The postpartum period was complicated by anemia, thrombocytopenia, epistaxis, and superficial wound hemorrhage.[76] Successful pregnancies have been reported following bone marrow transplantation in women with Fanconi anemia.[77]

Diamond-Blackfan anemia

Diamond-Blackfan anemia is an autosomal dominant congenital RBC aplasia resulting from failure of a single hematopoietic cell line. Treatment generally consists of RBC transfusion with iron chelation and oral corticosteroids.[78] Bone marrow transplantation is also successful. There are isolated reports of pregnancy in women with this disorder and the associated risks include C/S, low birth weight, and premature delivery.[79,80] There are a few reports of nonimmune hydrops occurring in the infants of mothers with Diamond-Blackfan anemia.[81,82]

Shwachman-Diamond (SD) syndrome

This is a very rare disorder. In 1999 there were approximately 200 reported cases of SD and most had not lived to age 16. There is a single report of successful pregnancy (delivery by C/S) in this autosomal recessive inherited bone marrow failure syndrome.[80] Women with this disorder have evidence of pancreatic insufficiency (steatorrhea, malabsorption), neutropenia, anemia and thrombocytopenia, short stature, and bony abnormalities. Supportive therapy is essential throughout pregnancy.

Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal disorder of bone marrow, which may affect young adults. An abnormal clone at the stem cell level produces RBCs, platelets, and granulocytes that are abnormally sensitive to complement.[4] This leads to acute and chronic intravascular hemolysis, intermittent hemoglobinuria, and a thrombotic tendency. Thrombocytopenia often occurs, while granulocytopenia (increased risk of infection) is less common. Some patients present with a picture indistinguishable from aplastic anemia. Bone marrow transplantation has been successful in curing PNH.

Venous thrombosis is frequent in PNH and is attributed to intravascular hemolysis with inappropriate activation of thrombin. Patients who have had episodes of thrombosis may be on long-term oral anticoagulation, which, in pregnancy, would be switched to therapeutic, subcutaneous heparin (unfractionated [UFH] or low-molecular-weight [LMWH]).[83] There is limited experience with this disorder in pregnancy; however, several reports describe severe thrombotic complications in unusual sites (maternal hepatic vein, cerebral venous sinus) and fetal loss.[84,85,86,87]

Washed RBCs should be given when transfusion is needed to correct anemia or during episodes of hemolysis.[85] Prophylactic transfusions may decrease the incidence of thrombotic complications, but this remains speculative because of the small number of patients with PNH and the inability to undertake properly structured research trials. Steroids are useful in approximately 50% of patients during acute hemolytic episodes.

Sideroblastic anemia

This is a descriptive term for a variety of disorders that have a defect in heme biosynthesis and defective iron use. They are inherited in either an autosomal recessive or sex-linked pattern

or acquired in association with certain diseases (myelodysplastic syndromes, malignancy), drugs, or toxins. Ringed sideroblasts in the bone marrow are diagnostic. Medical management during pregnancy is similar to the patient with hypoplastic anemia. However, since this disorder is associated with significant dyserythropoiesis, administration of exogenous iron is contraindicated unless the serum ferritin suggests iron deficiency, which is highly unlikely. There are few reports of pregnancy in patients with sideroblastic anemia. In one successful pregnancy the hematocrit was maintained throughout pregnancy by periodic transfusion of washed RBCs.[88] A woman with twin pregnancy required periodic transfusion when she had a relapse during pregnancy.[89]

Anesthesia for parturients with bone marrow failure disorders

The principles of management for these patients relate primarily to ensuring adequate oxygen-carrying capacity, prevention of infection, and, more importantly, adequate hemostasis.[90] A multidisciplinary approach is necessary for optimal management of their labor and delivery.

Patients who had previous transfusions or previous pregnancies are often refractory to platelet transfusions due to the presence of human leukocyte antigen (HLA) antibodies. Human leukocyte antigen typing of the patient in advance, and collection of HLA-matched platelets for support during delivery, is necessary. Similarly, patients who have received previous RBC transfusions may have red cell alloantibodies. Advance warning to the blood bank helps ensure availability of RBCs. Patients who have never had blood products and are potential candidates for bone marrow transplant require consultation with a hematologist and transplantation team to ensure that appropriate products are used in order not to compromise chances for a successful transplant.

Neuraxial anesthesia is contraindicated in the presence of severe thrombocytopenia, but there is little in the literature to guide one with respect to a "safe" platelet count in women with primary marrow disorders. A platelet count $>50 \times 10^9$/l is adequate for an uncomplicated vaginal delivery. However, in our opinion, a platelet count of 75–80 $\times 10^9$/l is required for adequate hemostasis prior to neuraxial anesthesia, episiotomy, or C/S in women with primary marrow disorders. This differs from the situation with idiopathic/immune thrombocytopenic purpura (ITP) where the platelets are young and healthy, as the thrombocytopenia is due to platelet destruction. In primary marrow disorders there is a mixture of old and young platelets in the circulation – the older platelets being less functional than young platelets.

In patients requiring transfusion of platelets to achieve adequate levels for delivery, a one-hour posttransfusion platelet count is essential to ensure that the target range has been reached. Failure to achieve a rise in platelet count of 5–10 $\times 10^9$/l per random donor unit of platelets transfused is suggestive of immune refractoriness, related to human leukocyte antigen (HLA) antibodies. The level of hemoglobin that is appropriate varies and depends on the degree of maternal compensation, fetal well-being, and projected blood loss.

It is important to provide adequate analgesia during labor as pain-induced hypertension could lead to intracranial hemorrhage in patients with severe thrombocytopenia. As regional anesthesia is contraindicated in the severely thrombocytopenic parturient, intravenous patient-controlled analgesia (PCA) with an opioid is an acceptable option. The neutropenia associated with marrow hypoplasia places the patient at increased risk of infection so appropriate precautions should be undertaken during invasive procedures, including surgery. Special considerations for bone marrow recipients are noted later in this chapter.

There are few reports of the anesthetic management of women with primary marrow disorders. There is a report of the anesthetic management of C/S in a woman with hypoplastic anemia and preeclampsia.[91] Immediately preoperatively her hemoglobin was 6.4 g/l, WBC count 4.33×10^9/l, and platelet count 10×10^9/l. She received ten units of platelets prior to induction of general anesthesia for C/S and four units intraoperatively. Hydralazine 5 mg was administered intravenously 20 minutes before induction, and alfentanil was administered prior to thiopental and succinylcholine in order to prevent a hypertensive response. The intraoperative course was uneventful.[89] Another report concerned a woman with myelodysplastic syndrome who had uneventful general anesthesia for C/S twice.[92]

Anesthetic considerations in women with PNH include strict asepsis, peripartum anticoagulation to prevent thrombosis, and prompt intervention in the event of hemorrhage, as well as maintenance of normothermia, normovolemia, acid-base balance, and avoidance of stress and medications that may activate complement release. Regional and general anesthesia have been described in patients with PNH.[87,93,94] Concerns with respect to general anesthesia include the risk of cerebral hemorrhage during induction in those with thrombocytopenia. Kjaer reported the use of general anesthesia in a parturient with PNH whose platelet count was 52×10^9/l.[94] Corticosteroids and blood products were administered after delivery of the placenta to avoid a hemolytic crisis. Heparin for antithrombosis prophylaxis was initiated postpartum.[94]

Although regional anesthesia has been described in patients with PNH, one must ensure there is an adequate platelet count, probably $>75 \times 10^9$/l. A report describes uneventful epidural labor analgesia in a woman whose platelet count was 64×10^9/l at the time of insertion. Epidural analgesia was used to reduce labor stress.[93] Paech and Pavy described the use of PCA intravenous fentanyl for labor analgesia in a woman with PNH followed by general anesthesia for removal of a retained placenta.[95]

Primary marrow malignant disorders

Philadelphia negative myeloproliferative diseases (MPD)

Most of these diseases occur in the 6th and 7th decades but they have been reported in younger women and in concurrence with pregnancy. The myeloproliferative disorders include, in order of appearance in the obstetric population: essential thrombocythemia (ET) (also known as essential thrombocytosis),

polycythemia rubra vera (PRV), chronic myelogenous or granulocytic leukemia, and myelofibrosis with myeloid metaplasia. All arise from clonal stem cell defects and these disorders are characterized by autonomous proliferation of the stem cell lines. Clinical features include thrombosis, hemorrhage, progression to myelofibrosis, and acute myeloid leukemia.[96] Management issues during pregnancy include maintenance of normal uterine blood flow and adequate placental development. The risk of thrombosis in the placenta and maternal circulation is high. Strategies during pregnancy include aspirin and/or heparin (LMWH or UFH) to prevent thrombosis, phlebotomy to reduce RBC or platelet mass, and possible use of cytoreductive agents such as interferon α and hydroxyurea. Occasionally, plateletpheresis is used.[96]

Essential thrombocythemia (ET)

This is the most common of the myeloproliferative disorders seen in pregnancy. These patients present with thrombocytosis that is often asymptomatic, particularly in the range below 1000×10^9/l. The criteria for diagnosis of ET is a platelet count consistently $>600 \times 10^9$/l, hematocrit <40, stainable iron in the marrow, a normal serum ferritin level, no Philadelphia chromosome, no evidence of marrow fibrosis, no cytogenic or morphological evidence of myelodysplastic syndrome, and no cause for reactive thrombocytosis.[97,98] At presentation, only 50% have splenomegaly and a sustained elevation of platelet count, usually $>1000 \times 10^9$/l. The platelet smear may be normal or show giant platelets and hypogranular platelets. Anemia is rare unless there has been hemorrhage or iron deficiency. The major causes of morbidity and mortality are thromboses (arterial and venous) and hemorrhage.[99] Stroke and transient ischemic attacks are common and are related to inappropriate platelet activation in the microvasculature. Symptoms requiring therapy are erythromelalgia (burning pain in the fingertips), headaches, easy bruising or mucous membrane hemorrhage. Interestingly, both thrombotic and hemorrhagic complications are usually controlled by lowering the platelet count. Platelet function studies fail to uncover a consistent pattern and there is no laboratory assay that predicts a predisposition to either bleeding or thrombosis. Some patients have spontaneous in vitro platelet aggregation or platelet hyperaggregability, while others lose platelet responsiveness to epinephrine.[100] Other platelet function abnormalities include platelet membrane abnormalities, acquired storage pool deficiency, and metabolic abnormalities.

In patients with evidence of platelet-associated thrombosis without impaired hemostasis, and a platelet count in the range of 1500×10^9/l or less, the use of low-dose aspirin is often sufficient to control symptoms.[98] Two major therapeutic options for ET are to lower the platelet count using antiproliferative agents, such as hydroxyurea or myleran (busulfan), or in the more acute situation, plateletpheresis. There is no concensus on the use of hydroxyurea or myleran during pregnancy.[100,101]

There have been over 280 pregnancies reported in 147 patients with ET. Essential thrombocythemia is accompanied by an increased risk of fetal complications, with early and late fetal loss rates approximately double that in the normal population. Other complications include IUGR, preterm delivery, and placental abruption. Although thrombosis is common, mainly in the postpartum period, hemorrhage also occurs (approximately 4–5%). In one review, two women with ET and acquired von Willebrand (VW) disease had major bleeding events.[102]

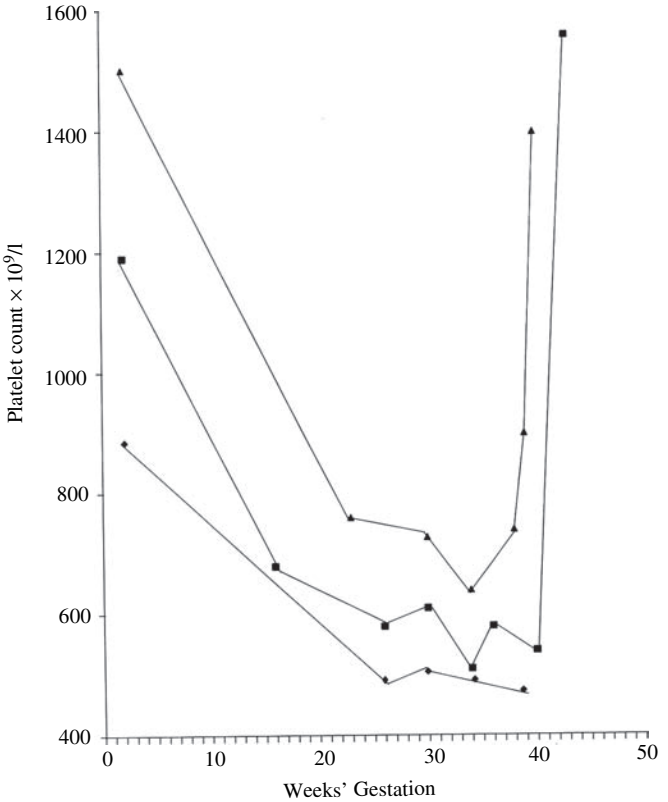

Figure 17.2 Platelet count of three patients with essential thrombocythemia demonstrating the physiological decrease in platelet count that occurred during pregnancy.

Randi *et al.* reported on six normal pregnancies in five untreated patients concluding that many patients do not warrant therapy during pregnancy.[103] In our experience, the platelet count decreases gradually during pregnancy, usually reaching its nadir at 32–36 weeks, coinciding with completion of plasma volume expansion (see Figure 17.2). Low-dose aspirin (81 mg daily) is reported to minimize placental compromise from platelet thrombosis. At the present time, there is no indication for routine heparin prophylaxis unless there is a preceding history of venous thrombosis. Women with very high platelet counts may be on interferon alpha (IFNα), which may reduce complications in any woman with ET. As IFNα is excreted in breast milk, breast-feeding is contraindicated in women receiving this therapy.

Polycythemia vera (PV, erythrocytosis)

This chronic myeloproliferative disorder, with an estimated incidence of 1:50 000 in the general population, is occasionally seen in pregnancy.[104] It is characterized by an increase in RBC mass, usually associated with a pancytosis and splenomegaly. Symptoms are related primarily to the increased blood volume and viscosity, and these patients are at risk from bleeding and thrombosis. These problems are well controlled

with phlebotomy.[104] Diagnosis is based on an elevated RBC mass, normal arterial oxygen saturation, and splenomegaly. If there is no splenomegaly two other criteria are required (leukocytosis $>12 \times 10^9$/l, thrombocytosis $>400 \times 10^9$/l, leukocyte alkaline phosphatase >100 U, serum B_{12} >900 pg/ml or unbound B_{12} binding capacity >2200 pg/ml).[104] Erythrocytosis may be primary (PV) or secondary (congenital, acquired).

Since PV is more common in men and older individuals, PV in pregnancy is uncommon. As of 2005, there were reports of 36 pregnancies in 18 patients with a neonatal survival rate of 50%. Complications included one maternal death after elective termination of pregnancy, two postpartum pulmonary emboli, and one large PPH. Four pregnancies were complicated by preeclampsia.[96]

Pregnant women with PV are at risk for poor obstetrical outcome because of placental compromise. Due to the autonomous nature of erythropoiesis in this disorder, the plasma volume expansion of pregnancy will result in a fall in hematocrit throughout the first 34 weeks with a nadir late in the third trimester.[96] Phlebotomy is safe during pregnancy and can be used to further reduce hematocrit, minimizing maternal and fetal risk. Iron stores will be diminished and careful limited supplementation may be necessary to ensure adequate iron delivery to the fetus. There is an increased risk of cardiac failure due to increased cardiac output associated with PV and pregnancy. Heparin may be used to reduce risk of thrombosis.[96]

Leukemia

Acute leukemia affects a younger population than does chronic leukemia. The incidence of acute leukemia is one in 75–100 000 pregnancies.[105] The majority of cases that occur during pregnancy are diagnosed during routine prenatal care. If acute leukemia presents during pregnancy, chemotherapy is generally started and is considered safe during the second and third trimesters,[106,107] but potential complications include hemorrhage and sepsis.[108] Remission rates are high following treatment of acute myelogenous and acute lymphocytic leukemia, but relapse is common within a year. Breast-feeding is contraindicated when the mother is receiving cytotoxic drugs.[109] Many parturients with leukemia have thrombocytopenia, hypofibrinogenemia, or DIC and so are at risk for hemorrhage. However, hemorrhage has rarely been reported possibly because these women tolerate low platelet counts well. Infection may be secondary to leukopenia from the leukemia, or from chemotherapy.

There is no evidence that pregnancy alters the incidence or prognosis of acute or chronic leukemia.[110] The commonest chronic leukemia during pregnancy (90%) is chronic myeloid leukemia (CML). Therapy during pregnancy is usually supportive; however, there are reports of treatment with interferon-α during pregnancy.[111]

Myelofibrosis

Myelofibrosis is an extremely rare disorder in pregnancy possibly because the outlook of this disorder is bleak. In the past myelofibrosis was thought to be the outcome of polycythemia vera but this is debated. By 2005 only four pregnancies in two patients had been reported.[96] There were two live births at 34 and 36 weeks' gestation and two stillbirths due to placental infarction at 27 and 30 weeks' gestation.[96] Anesthetic management is not reported.[112]

Lymphoma

Hodgkin disease is the most common lymphoproliferative disorder in young people and overall, lymphoma is the fourth most frequent cancer diagnosis among pregnant women.[113] The prevalence of non-Hodgkin lymphoma is unknown. Pregnancy does not appear to affect the natural history of Hodgkin disease[114] and vice versa. However, high grade lymphomas, including Burkitt lymphoma, are rapidly progressive and require aggressive intervention and treatment in pregnant women. Extra-dural presentations of non-Hodgkin lymphoma have been reported, including one that resulted in paraparesis following delivery.[115] Mediastinal non-Hodgkin lympomas have been reported during pregnancy causing cardiorespiratory compromise.[116,117]

Multiple myeloma

This hematological malignancy results from proliferation of a single clone of neoplastic plasma cells and is rare in pregnancy.[118,119,120,121,122] Clinically these patients may present with a spectrum of complaints including a mild unresponsive anemia, bone pain, pathologic fractures, neurologic deficits, and recurrent infections. Recurrent infections result from suppression of normal B cell function by the malignant clone. Spinal cord compression secondary to vertebral collapse with paraplegia occurs in approximately 14% of nonpregnant patients. Anemia occurs secondary to marrow infiltration and renal failure in the latter stages of the disease. An increased bleeding tendency may occur secondary to thrombocytopenia or through monoclonal protein interference with platelet function or coagulation factors. As well, these patients can develop a hyperviscosity syndrome with stroke, myocardial compromise, and skin infarction.

The cases reported in pregnancy had diverse presentations such as, threatened miscarriage,[121] anemia during a routine antenatal visit,[116] bilateral leg weakness and back pain postpartum,[118] and pathologic fracture.[122] The offspring were unaffected.

Waldenström macroglobulinemia

This disorder is characterized by an IgM monoclonal gammopathy and recurring purpura. Patients with this disorder have hepatosplenomegaly, frequently a mild anemia, and usually some degree of renal insufficiency. It is very rare in pregnancy with only one reported case.[123] That pregnancy was complicated by IUGR and fetal distress leading to C/S under general anesthesia. These patients usually have normal screening coagulation studies, a normal platelet count, and, in the absence of any

obvious purpura, a low bleeding risk. However, they may be at increased risk for thrombosis as a result of hyperviscosity related to the level of monoclonal IgM protein.

Anesthetic management for patients with malignant marrow disorders

Theoretically both regional and general anesthesia can be used in women with ET unless there is evidence of platelet dysfunction or ongoing hemorrhage, in which case regional anesthesia is contraindicated. In a patient presenting in the third trimester with a platelet count $>1500 \times 10^9$/l, consider urgent plateletpheresis to reduce the platelet count, minimizing the risk of thrombosis and bleeding. Postpartum, rebound severe thrombocytosis often occurs: this should be anticipated and intervention with chemotherapy and/or plateletpheresis, as well as low-dose aspirin, may minimize the risk of thrombosis.

There are multiple reports of women with ET undergoing C/S but there is only a single report of the anesthetic management.[124] In this case, coagulation was assessed at 38 weeks' gestation using TEG followed by uneventful epidural analgesia ten days later for labor analgesia. The authors noted that while TEG may be helpful, success in a single patient does not prove the safety of relying on TEG. Of note, at the time of the TEG, the woman had ecchymoses of her lower extremity and a platelet count $>1000 \times 10^9$/l. Based on these findings many anesthesiologists would consider neuraxial block contraindicated.

There are a few reports of anesthesia in the nonobstetric ET population, and they underline the importance of ensuring that preoperative platelet counts and platelet aggregation tests are within the normal range before considering neuraxial anesthesia.[125] As thrombosis is a major risk in patients with ET, consider thromboprophylaxis.[126] Invasive monitoring may be hazardous as there are reports in which radial artery thrombosis with subsequent necrosis followed radial artery catheterization in ET patients.[127,128] One case received spinal anesthesia,[127] and the other general anesthesia.[128]

In general, PV patients have a high risk of hemorrhagic and thrombotic complications related to surgery.[129] This is controlled by maintaining the hematocrit in the range of 0.40–0.45 with phlebotomy. In the event of emergency C/S, attention should be paid to positioning (to prevent venous stasis) and hemodilution should be performed, preferably with associated phlebotomy if the hematocrit is >0.45. Maintain normotension and provide supplemental oxygen.

Although the advantages of vasodilatation, improved regional blood flow, and hemodilution that occur with regional blockade and intravenous fluid preload are significant, regional anesthesia is avoided if the hematocrit is poorly controlled because of an unpredictable bleeding risk. Careful monitoring of fluids will prevent circulatory system overload, which could induce cardiac failure. There is one report of epidural anesthesia for C/S in a parturient with PV and preeclampsia.[130] During her pregnancy she was treated with IFNα and prednisone. Her coagulation profile was normal the day of surgery and the woman had uneventful regional anesthesia. The authors commented that the coagulation profile should be normal and acquired VW disease ruled out prior to administering neuraxial anesthesia.

Anesthetic management of patients with acute leukemia shares similar principles to that of aplastic anemia, since the complications of anesthesia and surgery relate to the pancytopenia associated with these disorders and/or their treatment. In patients with acute leukemia, aggressive large cell lymphoma, or chronic granulocytic leukemia (CGL) who remain untreated at the time of delivery, special attention must be given to the level of blast cell count or, in the case of CGL, the total WBC count. Significantly increased blast cell counts place the patient at risk for hyperviscosity syndrome leading to renal compromise, cerebral infarction, and other complications. Leukopheresis or rapid reduction of WBC count with chemotherapy may reduce the risks of anesthesia and labor. Vigorous hydration is essential with close monitoring of urine output and renal function. Although some of these women have delivered by C/S there is little information regarding anesthesia. Spencer and colleagues described a parturient with multiple medical issues (myocardial infarction, congestive heart failure, diabetes mellitus, asthma, two previous C/S, mild preeclampsia) in addition to CML, with suboptimal control.[131] The woman refused epidural anesthesia and general anesthesia was uneventful. There was no discussion regarding the implications of her poorly controlled leukemia.

Bucklin and coworkers reported a clinical dilemma whereby a parturient with acute myelogenous leukemia developed a postdural puncture headache (PDPH).[132] Although epidural blood patch was considered, symptomatic treatment was given due to concerns about the risk of infection and central nervous system leukemia. The PDPH resolved ten days after the dural puncture.

Anesthetic concerns in women with lymphoma relate to the degree of cardiorespiratory compromise,[116,117] and multidisciplinary involvement is essential. One patient with a mediastinal tumor, had a C/S five days following initiation of chemotherapy, thereby preceding the nadir of pancytopenia. As her condition was stable, uneventful epidural anesthesia was provided. Appropriate equipment was present in the operating room to manage any airway problems that might have arisen.[116] In another report,[117] a parturient with a 32-week twin gestation had recurrent upper gastrointestinal bleeding. She required emergency C/S under general anesthesia. Following delivery, during upper gastrointestinal endoscopy, difficulty with ventilation was noted and an emergent computed tomography (CT) scan demonstrated a non-Hodgkin lymphoma mediastinal mass.

Bone marrow transplantation

Pregnancy has been reported following bone marrow transplantation for aplastic anemia and hematologic malignancies,[133] but is relatively uncommon when total body irradiation (TBI) is given prior to transplant. Anesthetic management should focus on the

patient's current status as multiple sequelae may result from the procedure. The technique of choice for analgesia and anesthesia will be based on the current hematologic and clinical condition.[134] Total body irradiation and/or chemotherapy can produce pulmonary fibrosis so pulmonary function should be assessed. Strict aseptic technique is required as these patients are prone to infection. Generally speaking there is no contraindication to the use of general or regional anesthesia. These patients are at risk for both transfusion-associated infection and alloimmunization to RBCs and platelets.[135]

Coagulation disorders

In the past regional anesthesia was considered contraindicated in any patient with a bleeding abnormality, even if there was no evidence of overt bleeding or bruising. This applied to parturients with platelet counts $<100 \times 10^9$/l, mild VW disease and those treated with heparin and/or aspirin. With better understanding of the pathophysiology of these disorders and the changes that occur with pregnancy, anesthesiologists are becoming more liberal in their use of regional anesthesia. Within certain limitations, it is unlikely that this change will be accompanied by an increase in anesthetic-related complications.

The major concern with regional anesthesia relates to the development of a spinal or epidural hematoma with resulting permanent neurologic damage. The incidence of this complication in parturients is extremely low,[136,137,138] and it is difficult to determine the relationship between epidural hematoma, regional anesthesia, and coagulopathy.

For many coagulation disorders, there is no concensus as to the most appropriate anesthetic management. The obstetric literature indicates that patients with many of these unusual conditions have received anesthetic care. Some general principles for anesthetic management of the parturient with a coagulation disorder are outlined in Table 17.3.

Table 17.3 Principles of anesthetic management of patients with a bleeding disorder

1. Take a thorough history: emphasis on family history of bleeding, bruising (especially during surgery, dental work)
2. Do a thorough physical examination: bruising, bleeding, petechiae (blood pressure cuff, i.v. sites)
3. Lab work: CBC, platelet count, specific testing dependent on history, clinical course
4. Involve hematologist, if appropriate
5. Assess airway, feasibility of other techniques
6. Discuss risks/benefits of proposed procedure and what is known about risk
7. Discuss risks/benefits of blood products
8. Document discussion of 6 and 7
9. Proceed with regional anesthesia, if appropriate
10. Remember, if regional contraindicated so are pudendal block, intramuscular injections, NSAIDs, aspirin

CBC = complete blood count

Platelet disorders

Thrombocytopenia

Thrombocytopenia is the most common hematologic complication in pregnancy. The etiology varies from an apparent physiologic condition (gestational thrombocytopenia) to disorders associated with significant underlying pathology. The implications of a low platelet count with regard to anesthetic considerations in the pregnant woman vary according to the underlying pathophysiology of the thrombocytopenia (see Table 17.4).

Most authorities agree that the platelet count progressively decreases throughout gestation until 32–36 weeks, associated with a consistent increase in mean platelet volume.[11,12,139] This suggests an increase in platelet consumption (younger platelets being larger) but limited kinetic studies have failed to confirm a shortened platelet life span in pregnancy. A study of platelet behavior demonstrated an increase in platelet reactivity in the third trimester.[140] It should be remembered that platelet activation is the first stage of in vivo hemostasis. In patients with hypoplastic thrombocytopenia and platelet counts $<100 \times 10^9$/l, there is a relationship between platelet counts and the bleeding time.[141] In conditions such as ITP, this relationship is shifted to the left, and in patients with platelet dysfunction, to the right. The use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with any of these disorders can dramatically shift the relationship between platelet count and platelet function. Therefore, these drugs should not be used in patients with thrombocytopenia.

Table 17.4 Disorders of platelets during pregnancy

Disorder	Thrombocytopenia	Abnormal platelet function
Gestational thrombocytopenia	Yes	No
ITP	Yes	No
May Hegglin anomaly	Yes	Possibly
Antiphospholipid syndrome	Yes	Very unusual
HIV	Yes	No
Microangiopathic syndromes	Yes	Only, if significant decrease in fibrinogen
Bernard Soulier syndrome	Yes	Yes
Chediak Higashi syndrome	No	Yes
Platelet storage pool deficiency	No	Yes
Glazmann thrombasthenia	No	Yes
Von Willebrand disease	No, except with variant type IIB	Yes

ITP = idiopathic/immune thrombocytopenic purpura; HIV = human immunodeficiency virus

Gestational thrombocytopenia (incidental thrombocytopenia of pregnancy)

Gestational thrombocytopenia occurs in approximately 8% of all pregnant women.[142] It is generally mild with a platelet count greater than 90×10^9/l, although it may be lower. Patients and their neonates are not at increased risk of bleeding, and the platelet count in the majority of patients returns to normal three to five days postpartum. This pattern may be repeated in subsequent pregnancies.[143]

The diagnosis of gestational thrombocytopenia is usually one of exclusion. Diagnosis is based on a normal platelet count in early pregnancy, no previously documented thrombocytopenia prior to pregnancy, and the absence of clinical evidence for impending preeclampsia. Thrombocytopenia that occurs prior to pregnancy, or within the first trimester of pregnancy, is generally ITP. Parturients with uncomplicated gestational thrombocytopenia can have regional anesthesia safely.[144,145]

Idiopathic/immune thrombocytopenic purpura

This is a common disease in young women and has an incidence of approximately 0.01–0.02% of deliveries.[146] Studies on its pathophysiology have revealed the presence of platelet-specific autoantibodies (usually IgG), which recognize immunogenic glycoproteins on the platelet membrane. Generally speaking, thrombocytopenia is related to increased destruction of sensitized platelets in the RE system; however, there is also evidence for antibody-mediated impaired thrombopoiesis.[147,148] Laboratory findings usually include isolated thrombocytopenia (antedating pregnancy or presenting early in pregnancy) with large well-granulated platelets and often normal hemostasis in spite of a significantly reduced platelet count. Not infrequently, there is a family history of autoimmune disease. The most common conditions in the differential diagnosis include thrombocytopenia associated with SLE, human immunodeficiency virus (HIV) infection, and antiphospholipid antibodies. There is no specific laboratory test, and routine measurement of platelet antibodies is not recommended.[139] Rarely, there is a concomitant platelet functional abnormality.

There are insufficient data to recommend treatment of the asymptomatic parturient who has a platelet count above $20–30 \times 10^9$/l during the antenatal period.[139] At our institution, treatment (prednisone or IVIG) is administered when there is impaired hemostasis during pregnancy or to elevate the platelet count prior to delivery or an invasive procedure. Those patients who require therapy usually respond to prednisone 1 mg/kg or IVIG 2 g/kg over two to five days. Those who fail to respond to either therapy may respond to a combination of the two. Rarely splenectomy is required during pregnancy and is best done during the second trimester.

Infants born to mothers with ITP may be thrombocytopenic because the antibody crosses the placenta.[149,150] Approximately 5% of neonates born to mothers with ITP have significant thrombocytopenia ($<50 \times 10^9$/l) at birth; however, over the few days following birth, approximately 30–40% of neonates with a normal or near-normal count at delivery may become significantly thrombocytopenic. In the past, it was suggested that an assessment using percutaneous umbilical cord or fetal scalp-vein sampling of fetal platelets prior to delivery was appropriate in the small number of patients considered at high risk to deliver a severely affected infant.[151,152,153] Due to the high incidence of fetal mortality, these procedures are no longer recommended.[139] Neonates of ITP mothers should be followed daily until their platelet count has stabilized (usually within three days). Recent practice guidelines do not recommend routine C/S for women with ITP.[139]

In preparation for delivery, it is often appropriate to administer a short course of steroids or IVIG at 37–38 weeks' gestation to elevate the platelet count, ensuring a full range of options for analgesia in these patients. There is no role for platelet transfusion unless there is life-threatening bleeding. Aspirin and NSAIDs are contraindicated.

Anesthetic management of women with ITP is usually straightforward. In most instances platelet function is excellent and a platelet count of $>75 \times 10^9$/l is more than adequate for regional anesthesia. A history of a lack of bleeding problems at a given platelet count should reassure the anesthesiologist, and a careful physical examination will assess hemostasis prior to neuraxial block. Many anesthesiologists are comfortable administering neuraxial anesthesia, especially spinal anesthesia, to parturients with ITP and platelet counts between 50 and 75×10^9/l. In the past it was recommended that women not receive neuraxial block unless the platelet count was $>75–100 \times 10^9$/l but there is little evidence to support this practice.[21,139] In our center, women with ITP and platelet counts $>50 \times 10^9$/l are routinely offered regional anesthesia providing there are no other specific contraindications to its use. In special situations, such as fetal distress and a difficult maternal airway, platelet counts as low as 40×10^9/l may well be safe for spinal anesthesia (risk of neuraxial bleeding is less than risk of emergency general anesthesia).

Wiskott-Aldrich syndrome (WAS)

Wiskott-Aldrich syndrome is an X-linked recessive disease with a poorly understood pathophysiology. As it is X-linked, it is found mainly in males and is associated with developmental defects of platelets, lymphocytes, and possibly other bone marrow-derived cell lineages resulting in immunodeficiency, thrombocytopenia, eczema, and susceptibility to malignancies. Platelets are typically small and thrombocytopenia may cause severe bleeding, requiring platelet transfusions. Hematopoietic stem cell transplantation corrects the thrombocytopenia and the immunodeficiency.[154] Normally female carriers have no clinical signs, but occasionally females have microthrombocytes without other findings of the syndrome. There are two reports of females with Wiskott-Aldrich syndrome-related thrombocytopenia with a wide spectrum of platelet size, including giant platelets.[155,156] In one family, this disorder was transmitted in an autosomal dominant fashion.[155] To date, no pregnant women with this disorder have been reported.

Other causes of thrombocytopenia

There are several other causes of thrombocytopenia that are not pregnancy specific. Spurious thrombocytopenia results when

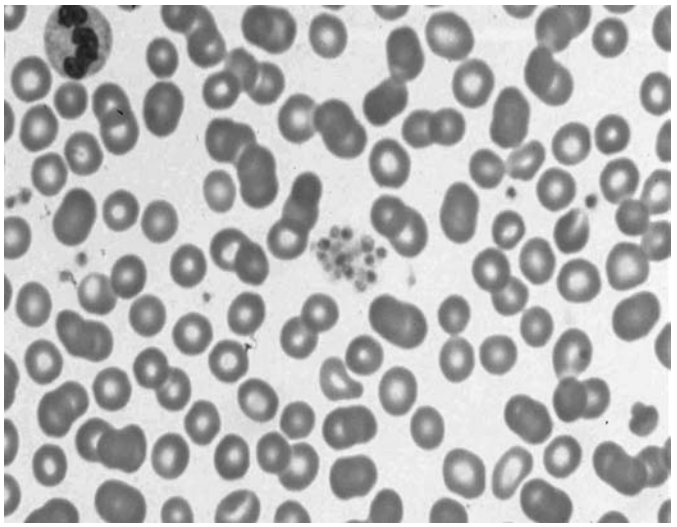

Figure 17.3 A peripheral blood smear demonstrating platelet clumping showing the comparative size of the clump with a white blood cell. (See color plate section.)

platelets are clumped and the automated counter "sees" them as WBCs. Review of the peripheral blood smear will result in a correct platelet count (see Figure 17.3). Thrombocytopenia may result from viral infections (HIV,[157] cytomegalovirus, Epstein Barr virus) and drug therapy (heparin, sulphonamides, penicillin, rifampicin, quinine).[158] Another cause of immune thrombocytopenia is that associated with antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, antibodies that cause a false positive serologic test for syphilis). Approximately 25% of patients with these antibodies have concomitant thrombocytopenia; however, the overriding risk is for thrombotic complications, rather than hemorrhage. These patients are at risk for a variety of adverse pregnancy outcomes, related mainly to placental compromise such as IUGR, abruption, severe and often early onset preeclampsia (<26 weeks' gestation), intrauterine death, placental infarction, recurrent miscarriage. The combination of low-dose heparin and low-dose aspirin (81 mg daily) is very successful and is currently the treatment of choice. In those who have suffered recurrent thrombosis prior to pregnancy necessitating long-term anticoagulation, therapeutic anticoagulation with heparin combined with aspirin is necessary throughout pregnancy. Providing these patients are not on therapeutic heparin, regional anesthesia is not contraindicated, but attention has to be paid to the timing of the block.[159]

Platelet functional disorders

Bernard-Soulier syndrome

This is a rare, autosomal recessive bleeding disorder characterized by low normal or diminished platelet count, giant platelets, and platelet dysfunction. Clinically, patients with this disorder have moderate to severe bleeding of the purpuric type. Very few pregnancies have been reported in women with this disorder.[160,161,162,163] Platelets from these patients have a deficiency of platelet glycoproteins Ib, IX and V. GPIb:IX is an important functional binding site on the platelet membrane for VW factor. Thus, GPIb-deficient platelets cannot bind to the subendothelium of the injured vessel in vivo. A prolonged bleeding time is characteristic of the disorder. Platelet aggregation studies reveal normal aggregation to ADP, collagen, and epinephrine but no response to ristocetin. Complications that occur during pregnancy include intrapartum bleeding and PPH (two to three weeks).[160,161] Platelet transfusions are ineffective if previous transfusion has resulted in alloimmunization to platelet glycoprotein Ib:IX. Furthermore, in the presence of this type of platelet specific antibody, the fetus may be at risk for immune-mediated thrombocytopenia, indistinguishable from neonatal alloimmune thrombocytopenia. There is one report of a successful pregnancy following treatment with IVIG.[160] In another report, a woman had post cesarean bleeding that required tranexamic acid; this report did not mention anesthesia.[162] These authors reviewed the literature for management during pregnancy and found 16 pregnancies in 9 women with this diagnosis. Postpartum hemorrhage (immediate, early, or delayed) occurred in all but three of the pregnancies. One case that did not report a PPH was an elective cesarean hysterectomy, as suitable platelet transfusion products were not available.[162]

Close involvement with a hematologist is important, particularly in the setting of an alloimmunized patient. Principles of anesthetic management include avoidance of invasive procedures such as intramuscular injections and regional anesthesia, including pudendal block. Platelet transfusion may be necessary if the patient is not alloimunized. Intravenous narcotic analgesia, nitrous oxide/oxygen in a 50:50 mixture for labor analgesia and general anesthesia for C/S are reasonable options. Aspirin and NSAIDs are contraindicated.

MYH9-related disease

Mutations in the MYH9 gene (responsible for nonmuscle myosin heavy chain IIA) on chromosome 22 result in autosomal dominant macrothrombocytopenias.[164] These disorders include May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome. Fechtner syndrome is similar to Alport syndrome in that nephritis, sensorineural hearing loss, and congenital cataracts are present. However, there is also macrothrombocytopenia and polymorphonuclear inclusions called Döhle-like bodies that are not present in Alport syndrome. Epstein syndrome does not have cataracts or Döhle-like bodies. Characteristics of May-Hegglin anomaly and Sebastian syndrome include thrombocytopenia, large platelets, and leukocyte inclusions, the latter differing in the two syndromes.[164,165] There are several reports of pregnancy in these various syndromes.[166,167]

May-Hegglin anomaly is a rare hereditary disorder characterized by giant platelets and blue inclusions in the cytoplasm of leukocytes. It is inherited as an autosomal dominant trait with variable penetrance. These patients have thrombocytopenia and platelet dysfunction. Platelet levels range from 10×10^9/l to normal levels and there may be a bleeding diathesis. Generally, these patients are asymptomatic but occasionally they have severe bleeding episodes related to thrombocytopenia.

There are several reports of pregnancy in patients with the May-Hegglin anomaly.[168,169,170,171,172,173] Most have delivered by C/S since the fetus, if affected, is at risk of intracranial hemorrhage. One case report documented a vaginal delivery after percutaneous umbilical blood sampling demonstrated a fetus with the May-Hegglin anomaly but an adequate platelet count.[173]

There is a report of general anesthesia for two C/S in one patient with May-Hegglin abnormality.[168] The patient had a low platelet count (approximately 80×10^9/l) and no evidence of bleeding. Spinal anesthesia for C/S was used following platelet transfusion in two other cases.[169,170]

Chediak-Higashi syndrome

This is a rare disease, which usually results in death before age ten. It is an autosomal recessive immunological disorder of neutrophil function. The syndrome is characterized by partial oculocutaneous albinism, decreased leukocyte chemotaxis, susceptibility to infection, and death in childhood. Neurological abnormalities may also occur: in particular, cerebellar involvement, peripheral neuropathies, and mental retardation.[174] It is a disorder of lysosome fusion and pathognomonic giant granules are seen in most biochemically active cells. A bleeding disorder related to platelet dysfunction occurs due to abnormalities of platelet content and aggregation.

There is one reported case of an uneventful pregnancy and vaginal delivery with no mention of anesthesia.[175] If there is a history or evidence of a bleeding disorder, regional anesthesia is contraindicated. These patients are susceptible to recurrent pulmonary infections, which may be resistant to antibiotic therapy, so strict asepsis is essential. Peripheral neuropathies producing muscle weakness and wasting may contraindicate the use of succinylcholine.

Glanzmann thrombasthenia (GT)

This very rare, life-threatening autosomal recessive bleeding disorder is characterized by qualitative or quantitative abnormalities of the platelet glycoprotein GPIIb and/or GPIIIa complex. These glycoproteins form a complex in the platelet membrane and act as a receptor for fibrinogen and other adhesive glycoproteins. Because of abnormalities in binding fibrinogen, severe platelet dysfunction may result with a failure of platelet plug formation. In vivo, platelets of these patients adhere normally to the subendothelium of damaged vessels, but there is defective recruitment of additional platelets via aggregation to form the hemostatic plug. In vitro, platelets agglutinate normally in the presence of ristocetin, but do not aggregate in response to other platelet agonists (ADP, collagen, thrombin, epinephrine, arachidonic acid).[176]

There are three types of GT: type I is associated with <5% normal GPIIb/IIIa; type II has 5–20% normal GPIIb/IIIa; the variant type has a qualitative defect in the GPIIb/IIIa complex. Few cases of pregnancy have been reported in patients with this disorder.[176,177,178,179,180] Patients with infants suspected of having GT are usually delivered by C/S to prevent intracranial hemorrhage. Women with GT often have multiple antiplatelet antibodies from previous platelet transfusions.[177] Antibody removal by plasmapheresis may be performed prior to platelet transfusion.

While bleeding can often be controlled using conservative measures (e.g. pressure), other agents such as topical thrombin, epsilon aminocaproic acid, and tranexamic acid may be required during surgery. There are reports of the use of recombinant factor VIIa in GT parturients.[178,179]

There also are reports of acquired GT whereby patients may present with no previous bleeding history and a normal platelet count but prolonged bleeding time. Acquired GT is often associated with lymphoproliferative or autoimmune disorders.[181]

In one report, a woman with GT received intravenous meperidine as neuraxial anesthesia was considered contraindicated.[176] In another report, a parturient with GT requiring urgent C/S received general anesthesia as TEG showed poor clot strength and she had alloimmunization to HLA.[180] The woman received gamma globulin the night before surgery and then prior to her surgery she received ten units of platelets and recombinant FVIIa. Intraoperatively, the woman received 12 units of platelets with TEG monitoring before and after administration. She continued to receive platelets and recombinant FVII prophylactically postpartum. Reported operative blood loss was 700–800 ml.

Platelet storage pool deficiency (SPD)

Platelet storage pool deficiency is a heterogeneous group of disorders that have in common platelets that have decreased adenosine diphosphate (ADP) in dense granules and/or decreased α-granule contents.[182] There are three types of platelet storage pool deficiency: those with deficiencies in the dense granules (δ SPD), α- granules (α SPD), or both types of granules (αδ SPD). These rare conditions are transmitted in an autosomal dominant pattern and produce a bleeding diathesis, which may be mild or severe. There is reduced ADP, ATP, serotonin, and calcium in the dense storage granules of platelets. Hermansky-Pudlak syndrome (HPS) is an inherited autosomal recessive disorder that manifests as oculocutaneous albinism, platelet storage pool deficiency (δ SPD), and intralysosomal ceroid lipofuscin accumulation.[183] The platelet count is generally normal in this condition although impaired platelet aggregation may lead to a hemorrhagic diathesis. Some patients with HPS develop pulmonary fibrosis, which is fatal in the fourth to sixth decades. Grey platelet syndrome (α SPD) is a rare inherited qualitative disorder of platelet function that results in bleeding.[184] The name derives from the grey appearance that is visible on Wright staining. The platelets are large, have a decreased number of cytoplasmic granules (alpha granules), and increased vacuoles resulting in abnormalities of platelet secretion and secondary aggregation. Thrombocytopenia may also be present.

There are few reports of pregnancy in women with platelet storage pool deficiency. In one report, there was a family history of bleeding and the patient had a previous hospital admission for bruising and epistaxis.[185] Labor was induced at 39 weeks' (platelet count 137×10^9/l) and leukocyte-poor platelets were infused during and after delivery to prevent hemorrhage. In one case report of a parturient with HPS, the woman received a platelet transfusion during active labor. Intravenous butorphanol was used for labor analgesia.[183]

Synthetic 1-deamino-8-d-arginine vasopressin (DDAVP) has been used in some of these patients to enhance coagulation. If platelet infusions are given, leukocyte-poor preparations should be used to decrease antibody development.

Principles of anesthetic management in parturients with platelet storage pool deficiency include avoidance of invasive procedures, where possible, and involvement of a hematologist in the event that the mother is alloimmunized. Regional anesthesia, including pudendal block, is best avoided. Intravenous narcotic analgesia, nitrous oxide/oxygen in a 50:50 mixture for labor analgesia, and general anesthesia for C/S are the therapies of choice. Avoid intramuscular injections, aspirin, and NSAIDs.

There is one report of anesthesia in two sisters with grey platelet syndrome (GPS).[184] The first sister required general anesthesia for an emergency C/S complicated by severe hemorrhage. The second sister had a primary C/S under spinal anesthesia for oligohydramnios. At that time, the diagnosis of GPS had not been made in the first sister. Following the diagnosis of GPS the second sister had another pregnancy and a repeat C/S following a failed trial of labor. General anesthesia was administered following platelet transfusion.[184]

There are reports on the use of intravenous PCA during labor using remifentanil in parturients with platelet abnormalities.[186] Remifentanil has the advantage of a short half-life and so is unlikely to affect neonatal respiration. However, interindividual variability and that same short half-life may make it difficult to balance adequate maternal analgesia with respiratory depression.

Thrombotic microangiopathy in pregnancy and the postpartum period

The microangiopathic syndromes seen in pregnancy and the puerperium are preeclampsia, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), acute fatty liver of pregnancy, and lupus vasculitis.[187] The peripheral blood smear in these syndromes shows hemolysis (schistocytes and fragmented cells) and thrombocytopenia (see Figure 17.4).

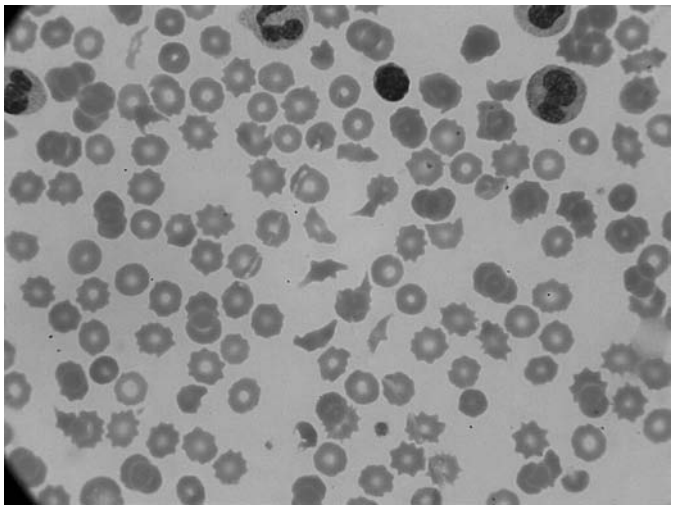

Figure 17.4 A peripheral blood smear from a patient with a microangiopathic syndrome demonstrating fragmented cells, schistocytes, and thrombocytopenia. (See color plate section.)

Preeclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome

A small group of patients with preeclampsia develop the HELLP syndrome.[188,189] These patients usually present preterm, although 30% may present postpartum, with malaise, epigastric or right upper-quadrant pain, and nausea/vomiting. Hypertension and proteinuria are not always prominent features. Hemolysis, elevated liver enzymes, and low platelets syndrome is associated with a high rate of maternal and perinatal mortality and treatment is delivery of the fetus. In one prospective study, morbidity associated with HELLP included DIC 18%, abruptio placentae 16%, acute renal failure 7.7%, pulmonary edema 6%, subcapsular liver hematoma 0.9%, and retinal detachment 0.9%.[190] Fifty-five percent required transfusion with blood or blood products. Patients who developed postpartum HELLP had a higher incidence of pulmonary edema and renal failure.[191]

The thrombocytopenia may be severe ($<20 \times 10^9$/l), with the nadir in platelet count occurring postpartum. Recovery to platelet counts $>100 \times 10^9$/l may take up to 11 days.[192,193] Providing there is no associated DIC, hemostasis is frequently normal until the platelet count is $<40 \times 10^9$/l.[194] However, the platelet count may fall precipitously leading to clinical bleeding in a short period of time. It is essential to assess the course of the thrombocytopenia and the clinical picture. If the platelet count has been stable at 80×10^9/l and there is no evidence of bleeding, regional anesthesia may be considered. If, however, the platelet count was 120×10^9/l one hour previously and now is 80×10^9/l, regional anesthesia may be inappropriate. High-dose steroids have been used to treat preterm HELLP syndrome with a view to improving the platelet count to a level that will allow the patient to become a candidate for regional analgesia.[195]

In the past, concern was raised about platelet function in this disorder due to studies comparing platelet count and bleeding time. As these studies found no correlation between bleeding time and platelet count in HELLP syndrome, regional anesthesia was considered contraindicated in patients with a platelet count $<100 \times 10^9$/l.[196,197] Most now agree that the bleeding time is not an accurate measure of the risk of bleeding. Thromboelastography (TEG) is being used in some centers in these patients and has been found a useful technique.[198] However, due to the rarity of an epidural hematoma considerable experience will have to be gained with TEG to demonstrate its efficacy in determining the risk of an epidural hematoma in any individual patient. As regional anesthesia has definite advantages in patients with preeclampsia (improves intervillous blood flow, avoids potential difficult intubation), the risks and benefits of the procedure have to be weighed in each patient with HELLP syndrome.[199,200]

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (HUS) are both characterized by thrombocytopenia, microangiopathic hemolytic anemia, and ischemia of various

organs due to platelet aggregation in the arterial microvasculature.[201] Neurological dysfunction is said to be more common with TTP while renal dysfunction is more common with HUS, although some patients have neither. Although often considered as separate disorders, many now consider them to be variants of the same disorder.[202] TTP/HUS is a rare disorder (1/100 000) that tends to occur primarily in young women, increasing the chance of its concurrence with pregnancy. Although TTP/HUS can occur throughout pregnancy, it occurs most commonly at term (TTP) and in the postpartum period (HUS). Microangiopathic hemolytic anemia and thrombocytopenia are essential to the diagnosis. The incidence of TTP in the USA is estimated to be 3.7 cases per million people and may be increasing.[201] The cause is either a deficiency of, or an inhibitor to, VW factor cleaving protease.[201] TTP/HUS probably has multiple pathogenic mechanisms that produce thrombi in the microvasculature and/or endothelial cell injury.[201] Since HELLP syndrome and TTP/HUS share significant clinical and laboratory features it is important to differentiate between the two, as the treatment is vastly different.[203] Hematological manifestations are generally milder in patients with preeclampsia and HELLP in contrast to those with TTP/HUS. A platelet count $<20 \times 10^9$/l favors the diagnosis of TTP providing there is no evidence of DIC. Some report that the plasma antithrombin III level is reduced in preeclampsia and normal in TTP.[201] The primary treatment of HELLP is delivery and possibly platelet or plasma transfusion. In contrast, continuation of the pregnancy and aggressive treatment of the mother using plasma exchange with frozen plasma is appropriate in antepartum TTP.[203] The use of platelet transfusions in TTP may result in a dramatic worsening of the condition from massive thrombosis.

Thrombocytopenia in TTP may be severe and in a small number of patients there may be a history of previous episodes. Prior to the use of plasma exchange, maternal and fetal mortality were very high.[203] Hayward and colleagues reviewed all cases of TTP in adults at their hospital.[204] There were nine treated patients of whom one died from "brain death", despite achieving hematologic remission. The others had a complete remission of TTP but most developed long-term complications. One was lost to long-term follow-up and of the remaining seven, only one was completely well. The others suffered mild renal impairment, persistent hypertension, persistent memory loss and hemiparesis, subsequent relapses, optic nerve infarct, and/or persistent myalgias and arthralgias.[204]

Thrombolytic thrombocytopenic purpura may occur postpartum[205] and there also appears to be a familial form of relapsing TTP.[202] Although TTP may have been successfully treated and in remission, it may also recur during pregnancy.[202] The overall prognosis improves with plasma exchange.[203]

Management of analgesia/anesthesia for TTP/HUS

To date, there have been no reports of anesthetic management of the parturient with TTP/HUS. However, there is an excellent review of the principles involved.[206] Although it is optimal to stabilize a woman with TTP prior to delivery, parturients with TTP that is active at delivery may have severe thrombocytopenia and a significant bleeding diathesis. Regional anesthesia and intramuscular injections should be avoided. Due to concerns about neurologic function sedatives should be avoided or used with caution. These patients are prone to seizures and appropriate precautions should be taken. Platelet transfusions should be avoided and packed RBCs and frozen plasma should be administered through a large-bore catheter. Patients who have received multiple plasma exchanges may have an arteriovenous (AV) shunt and this should be managed appropriately. Careful management of intravascular volume and sustaining a good urine output are important to avoid any further renal insult.

Intravenous PCA or nurse-administered narcotic analgesia, and nitrous oxide/oxygen are useful techniques for labor analgesia. For C/S, general anesthesia with special attention to gentle manipulation of the airway is advisable, especially if the platelet count is less than 50×10^9/l. Hypertension on intubation should be avoided, if possible, in patients with low platelet counts due to the risk of intracranial hemorrhage, as should hypotension due to potential renal involvement.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is a relatively rare disease of unknown etiology, which may present with malaise, nausea, vomiting, and upper abdominal pain.[207,208] There is rapid progression over a one to two week period to overt liver failure with jaundice and bleeding. Further deterioration may lead to seizures, coma, and death.[209,210] Studies of liver function will point to signs of hepatic failure (hypoglycemia, markedly elevated direct bilirubin, alanine aminotransferases, blood ammonia, and often rising blood urea nitrogen and creatinine). The peripheral smear is similar to those of other microangiopathic disorders; however, there are decreased antithrombin III levels and marked prolongation of PT and aPTT, and hypofibrinogenemia. Treatment should consist of aggressive support to address the hypoglycemia and coagulopathy, with careful fluid and electrolyte management, and treatment of associated seizures.[208] For anesthetic considerations see Chapter 14.

Miscellaneous platelet disorders

Sticky platelet syndrome

Sticky platelet syndrome (SPS) is inherited as an autosomal dominant disorder and is associated with arterial and venous thromboembolic disease.[211] Clinically, women may have angina, acute myocardial infarction (MI), transient cerebral ischemic attacks, stroke, and thrombosis in the arterial and venous systems. There is one report of a 24-year-old woman who had a MI during her pregnancy.[211] There were no identifiable risk factors except for her mother who had an acute MI during pregnancy, and an 18-year-old brother with angina. Laboratory testing revealed that her platelets and those of her symptomatic family members were hyperaggregable with ADP and epinephrine. Treatment of the family resulted in normal platelet aggregation. There was no information reported regarding the mode of delivery or

anesthetic management. However, as platelet aggregation is normal when these patients are on low-dose aspirin (81 mg), women with SPS should be regarded as normal in regards to their anesthetic management. Other families with venous and arterial thromboembolism and no other known risk factors have been identified with SPS.

Neonatal alloimmune thrombocytopenia (NAIT)

This disorder is caused by transplacental passage of maternal platelet-specific alloantibodies directed against specific antigens present on fetal but not maternal platelets. As a result, the fetus/neonate may be affected with severe thrombocytopenia, which may be associated with massive intracranial hemorrhage leading to significant morbidity/mortality. Neonatal alloimmune thrombocytopenia is the platelet equivalent of rhesus (Rh) disease; however, unlike erythroblastosis fetalis, NAIT occurs more commonly in the first pregnancy. The incidence of neonatal intracranial hemorrhage is 15–20% with half of these occurring antenatally. Early diagnosis and treatment of the mother with weekly high-dose IVIG from approximately 20 weeks' gestation has dramatically improved the fetal and neonatal mortality and morbidity associated with this disorder.

Since this disease affects the fetus and not the mother, analgesia/anesthesia for delivery is dependent on the mother's wishes and overall clinical condition. However, preparation of compatible maternal or homologous platelets is important to ensure their availability for the infant at delivery.

Blood vessel wall disorders

Bleeding from disorders of the blood vessel wall is usually mild and superficial. Inherited blood vessel wall disorders are rare and there is limited information about these patients in pregnancy. A careful history and, when indicated, a careful assessment, preferably prior to pregnancy or at least well in advance of delivery, is necessary to fully assess the extent of the disease and its implications for anesthesiologists. Acquired blood vessel wall disorders are much more common and for the most part fall into the category of vascular purpura, which arises from damage to the endothelium or its supporting matrix. There is very little literature on the anesthetic implications in pregnancy. A careful physical examination to assess the presence of active purpura will provide the best assessment of bleeding risk.

Hereditary hemorrhagic telangiectasia (HHT, Osler-Weber-Rendu syndrome)

Hereditary hemorrhagic telangiectasia is inherited as an autosomal dominant disease and is characterized by abnormal small blood vessels and AV fistulae involving almost all organs. The telangiectasia often appear as small blush areas on the skin, and mucous membrane involvement commonly presents as epistaxis or gastrointestinal hemorrhage. Pulmonary arteriovenous malformations (AVM) are present in at least 30% of patients with HHT, while hepatic and cerebral AVM are present 30% and 10–20% respectively.[212] The physiological changes of pregnancy accentuate the AV shunts due to dilation of the systemic vascular bed, increased blood volume, and increased cardiac output while hormonal changes may weaken the vessel walls.[213,214] Reports of deterioration of pulmonary AVM during pregnancy indicate that these patients should be followed closely to decrease the risk of maternal morbidity.[215,216,217] In one report, transcatheter embolic therapy was used in a pregnant woman with pulmonary AVM.[216] Hemothorax has been reported during pregnancy secondary to lung involvement,[213] and arterial hypoxemia and paradoxical embolism may reflect pulmonary shunts.[216] Congestive cardiac failure due to hepatic AV shunts and portal hypertension have occurred during pregnancy.[218] Fistulas have been reported in the epidural space and in the spinal cord (see Chapter 3).

Pseudoxanthoma elasticum (PXE)

Pseudoxanthoma elasticum is an inherited connective tissue disorder with biosynthesis of abnormal collagen and elastin fibers, which may result in hemorrhage and thrombosis. Some authors question whether PXE deteriorates during pregnancy,[219,220,221] although one report suggested that most pregnancies with PXE are uncomplicated.[222] Gastrointestinal hemorrhage may occur and there is an increased incidence of cardiac dysrhythmias.

Allergic purpura (Henoch-Schönlein purpura, HSP, Schönlein-Henoch purpura, SHP)

This IgA-mediated vasculitis commonly affects the kidneys, joints, gastrointestinal system, and the skin and is mainly a disease of children although several cases have been reported in pregnancy.[223] The clinical syndrome of purpura, hematuria, proteinuria, abdominal pain, gastrointestinal bleeding, and arthralgia is due to a generalized vasculitis. It appears to be allergic in origin but often an etiologic agent is not identified. The effect of pregnancy on HSP is unknown, although one study suggests that pregnancy may be a trigger for new-onset or recurrence of HSP in susceptible individuals.[224] Plasmapheresis has been used to treat severe relapses during pregnancy, resulting in a successful outcome for mother and fetus.

Anesthetic management of women with vessel wall abnormalities

In all of these disorders anesthetic management is dependent on the status of the patient. There are no specific contraindications to regional anesthesia, but if there is ongoing hemorrhage regional anesthesia is contraindicated. In many of these disorders, abnormal spinal and epidural vessels may be present increasing the chance of venipuncture with subsequent bleeding into the epidural space. In each situation, the risk and benefit of the procedure will determine whether, following appropriate informed consent, regional or general anesthesia should be used. If regional anesthesia is chosen, these patients should be followed closely for possible neurological sequelae. To decrease risk associated with the procedure, the most experienced person

should perform the block and it should be done in the midline. The risks and benefits of the alternatives should be considered for each patient.

There is one case report of uneventful epidural anesthesia in a laboring parturient with HHT.[213] Analgesia, with the subsequent decrease in catecholamines attenuating the increased cardiac output from labor, was considered important in decreasing distension of existing AV fistulae. As there is the potential for paradoxical embolism through pulmonary fistulae, the epidural space should be identified using loss of resistance to saline.

There are two reports of uneventful epidural anesthesia in parturients with PXE.[225,226] The major risk during pregnancy is related to gastrointestinal hemorrhage, but most reports indicate an uneventful labor and delivery. Levitt and Collison reported a difficult intubation in a nonpregnant patient with PXE.[227] The authors suggested that the problem was secondary to calcification and aggregation of elastic fibers in the laryngeal ligaments and cartilage.

Factor deficiencies

There are several excellent reviews on this subject.[16,228,229,230,231]

Fibrinogen (factor I, FI) deficiency

Fibrinogen is a protein synthesized in the liver with a half-life of approximately four days. Fibrinogen is necessary for normal platelet aggregation and a functional fibrinogen level <0.5 g/l is associated with microvascular bleeding. There are three congenital abnormalities of fibrinogen deficiency: afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia.[16] In afibrinogenemia there is a total absence of fibrinogen; hypofibrinogenemia refers to a decreased level of normally functioning fibrinogen; while in dysfibrinogenemia the fibrinogen is functionally abnormal.

Afibrinogenemia is inherited in an autosomal recessive manner and is due to defective synthesis. Afibrinogenemia has a prevalence 1:1 000 000 and is often associated with consanguinity. Bleeding due to afibrinogenemia may be life threatening but there are long periods where there is no bleeding. Bleeding associated with hypofibrinogenemia is generally milder and may follow invasive procedures, such as surgery. Women with afibrinogenemia and hypofibrinogenemia may have recurrent pregnancy loss as well as antepartum and postpartum hemorrhage and thromboembolism.

Some women with dysfibrinogenemia are asymptomatic while others will have episodes of hemorrhage or thrombosis. Bleeding may not correlate with the fibrinogen level or thrombin time. Fibrinogen deficiency can also be acquired. Treatment of afibrinogenemia is fibrinogen concentrate. Some authors recommend using fibrinogen concentrate prophylactically throughout pregnancy beginning once pregnancy is confirmed.[16] Fibrinogen concentrate may be ineffective in women with dysfibrinogenemia, while other measures such as topical fibrin glue or tranexamic acid may be useful. Avoid invasive monitoring and procedures on the fetus in women with dysfibrinogenemia as it is assumed that the fetus will also have dysfibrinogenemia. Women who are asymptomatic may simply be followed closely.

In a review of pregnancy in women with congenital dysfibrinogenemia, 55% were asymptomatic, 25% had a bleeding tendency, and 20% a thrombotic tendency.[232] The prevalence of dysfibrinogenemia in patients with a history of thrombosis is low, 0.8%. In pregnancy, severe bleeding is rare and is usually limited to the postpartum period. Women with a thrombotic tendency have a high incidence of spontaneous abortion and postpartum thrombosis.

For the most part the problem with these patients is that of hemorrhage.[233,234] Periodic transfusions of fibrinogen may be necessary during pregnancy in order to prevent miscarriage. In patients with evidence of thrombophilia, low-dose heparin may be required for prophylaxis. It is important that these patients are identified early in pregnancy and a plan is devised by the hematologist, obstetrician, and anesthesiologist. Regional anesthesia is contraindicated.

Factor II (FII, prothrombin) deficiency

Factor II (prothrombin) is a glycoprotein synthesized in the liver. Along with factors VII, IX, and X, it is vitamin K-dependent. Factor II is necessary for conversion of fibrinogen to fibrin, aggregation of platelets, activation of plasminogen, activation of thrombin-activatable fibrinolysis inhibitor, activation of factors V, VIII, XI, and XIII, and activation of protein C in the presence of thrombomodulin. Factor Xa activates FII on the surface of platelets in the presence of FV and calcium.

Factor II deficiency is the rarest inherited bleeding disorder with a prevalence of 1:2 000 000.[16] It is inherited in an autosomal recessive manner and is often seen in situations of consanguinity. There are two types of FII deficiency: type I (hypoprothrombinemia – where antigen and activity levels are low) and type II (dysprothrombinemia – where antigen levels are normal but activity is low). Patients with type I deficiency often have mucosal and soft tissue bleeding as well as hemarthrosis. The PT and aPTT may be prolonged (see Table 17.2) but are occasionally normal; thus, if this disorder is suspected clinically, further testing is required.[235]

Obstetric complications in women with hypoprothrombinemia include spontaneous fetal loss and PPH.[236] Bleeding in type II deficiency is usually more variable, and these women may be asymptomatic or have mild bleeding symptoms.

Factor V (FV) deficiency

Factor V is a large glycoprotein that is synthesized in the liver and in megakaryocytes.[16] Platelets normally contain approximately 20% of the circulating FV. Factor V is activated by thrombin and acts as a cofactor for FXa in converting prothrombin to thrombin (FII to FIIa). Factor Va is downregulated by activated protein C to maintain normal hemostatis.

Factor V deficiency is a rare autosomal recessive disorder with a prevalence of 1:1 000 000 that is often seen in consanguinous situations. In the homozygous state, there may be moderate to

severe bleeding. Postpartum hemorrhage has been reported in pregnant women with this disorder. Laboratory testing will show a prolonged PT and aPTT with a normal thrombin time (see Table 17.2). The abnormal PT and aPTT can be corrected by mixing the patient's serum with normal serum. Treatment of bleeding episodes is with fresh frozen plasma (FFP).

There are few reports of FV deficiency in pregnancy. A retrospective report described the experience of pregnancy and the use of oral contraceptives in women with FV deficiency (homozygous and heterozygous).[237] There were five homozygous patients and two of these had a total of three pregnancies. One of these was known to have FV deficiency and received prophylactic FFP two hours before C/S; this was followed by repeat transfusion of FFP for five days postpartum. No mention is made of anesthesia and no details are given regarding her other pregnancy, which presumably was managed in a similar fashion. In the other woman, FV deficiency was detected following excess bleeding at delivery. In heterozygotes, 15 pregnancies in 11 women were uneventful.[237] In another report a women had undetectable FV levels and although she had minimal bleeding problems (bruising and occasional epistaxis) she was advised not to have an epidural.[238] She had an emergency C/S under general anesthesia and received two units of solvent-detergent plasma. There was minimal blood loss during surgery or postpartum. Bolton-Maggs *et al*. recommend FFP once the woman is in established labor followed by monitoring of FV levels.[16] However, one may wish to use solvent-detergent plasma rather than FFP due to the lower risk of transmitting infection. As with any blood products, inhibitors to the factors may develop so the number of blood products should be limited.

Factor VII (FVII) deficiency

Factor VII is a vitamin K-dependent plasma glycoprotein that has a half-life of approximately three to six hours.[16] In the extrinsic system, FVII interacts with tissue factor to accelerate the hydrolysis of FX, converting prothrombin to thrombin to form a permanent fibrin clot. Factor VII deficiency is inherited in an autosomal recessive fashion and severe deficiency (FVII: C $<$ 2 IU/dl) has a prevalence of approximately 1:300–500 000.[239] Laboratory testing reveals a prolonged PT that corrects with 50:50 mix normal plasma, providing there is not an inhibitor. Activated partial thromboplastin time, TT, and fibrinogen levels are normal. One should exclude vitamin K deficiency as a cause of bleeding.

An FVII level less than 10% is indicative of homozygosity, but it is important to know that bleeding does not necessarily correlate with FVII level. In a study examining the surgical bleeding experience of individuals with FVII deficiency (FVII:C $<$ 0.01 IU/ml) who did not receive preoperative replacement therapy, the best predictor for risk of bleeding was clinical data (history of spontaneous joint bleeding), not laboratory values.[240]

Acquired FVII deficiency can occur secondary to vitamin K deficiency. This is usually associated with liver disease or vitamin K antagonists, such as warfarin. Treatment of bleeding in FVII deficient individuals is generally with recombinant factor VIIa (rVIIa), although plasma and FIX and FVII concentrates have been used. Thrombosis has also been reported in association with FVII deficiency with speculation as to the reason.[16,241]

In normal women, FVII levels increase during pregnancy, but it is unclear whether this happens in women with FVII deficiency. Several reports of management of FVII deficient pregnant women have been published, and recent reports highlight the prophylactic use of rVIIa to prevent hemorrhage.[242,243,244] There is a report of rVIIa administration prior to induction of epidural anesthesia for C/S.[245] The rVIIa infusion was continued for four days postpartum without complications. The literature is otherwise silent on the anesthetic management of patients with FVII deficiency. Obviously, if there is evidence of a coagulopathy (prolonged PT or INR), neuraxial anesthesia is contraindicated and options for labor include intravenous opioids and for cesarean delivery, general anesthesia.

Von Willebrand disease

Von Willebrand disease is the most common inherited bleeding disorder with a prevalence in the general population of 1%.[246] It has an autosomal dominant pattern of inheritance and is seen equally in males and females. Unlike hemophilia, phenotypic expression of VW disease varies within families. Approximately 90% of patients classify as type 1, which is characterized by a decrease in the level of plasma FVIII:VWF antigen and activity.[247] The other subtypes of VW disease (IIa, IIb, IIM, IIN, III, platelet) involve abnormal configurations of the multimer and varying abnormalities of plasma- and platelet-associated VWF.[247] The majority of those patients who are not type I are type II variants. Type III VW disease has a prevalence of 1:1 000 000. If the clinical history is strongly suggestive of this disorder then testing for abnormalities of the VWF/FVIII complex should be done on at least two separate occasions if initial results are inconclusive.

Thrombocytopenia may accompany VW disease variant type IIb and is thought to result from binding of the abnormal VWF to platelets with subsequent platelet aggregate formation and clearance.[247] It may prove difficult to distinguish between the thrombocytopenia of preeclampsia and variant VW disease.

Von Willebrand factor is synthesized in the endothelial cell and as plasma levels of VWF rise during pregnancy[248] many patients achieve clinical and laboratory remission. For those patients who require treatment, DDAVP at a dose of 0.3 μg/kg (maximum 20 μg total) is the treatment of choice with the exception of patients with VW disease types IIb and III.[249] Infusion of DDAVP results in an instantaneous release of VWF from the endothelium and an immediate two- to three-fold rise in plasma levels for both FVIII:C and VWF. However, repeated infusions can cause hyponatremia (occasionally resulting in seizures), as well as a tachyphylaxis. Thus, in practice, DDAVP infusions are usually only repeated once or twice at 12-hour intervals after the initial infusion. Patients with type IIb VW disease are at risk for worsening of their thrombocytopenia with infusion of DDAVP. For these patients and those with type III (the most severe form of VW disease), the use of Humate P (a viral inactivated plasma-derived product containing both FVIII:C and active VWF) is the treatment of choice.[247,249,250]

Factor VIII (FVIII) deficiency (hemophilia A)

This is an X-linked recessive trait, which results in deficiency (activity level of 35% or less) of FVIII.[230] Due to the X-linkage, affected females are very rare. Factor VIII is produced mainly in the liver and is a cofactor that markedly enhances activated FIX on the surface of platelets. The clinical severity of bleeding correlates with FVIII levels (see Table 17.5).

Due to lyonization (inactivation) of one of the X chromosomes in women, 10–30% of nonpregnant carriers may have low levels of FVIII activity and are at risk for bleeding complications (usually at surgery).[230] Fortunately, FVIII:C increases in pregnancy and, therefore, in the small number of carriers with symptomatic disease, remission usually occurs in pregnancy.[251] However, if the levels remain low these patients are at risk of hemorrhage.

There are two reports of pregnancy in women with severe FVIII deficiency.[252,253] In one report, the woman (FVIII level <0.3 U/ml) received recombinant FVIII concentrate once or twice weekly throughout her pregnancy.[252] A continuous infusion of recombinant FVIII was administered throughout labor to maintain the plasma FVIII level at normal levels. She received an epidural after coagulation was determined to be normal and had a spontaneous uncomplicated vaginal delivery.[252] In another case of hemophilia A (level <4%), the woman had a C/S for breech presentation.[253] Preoperatively, her FVIII level was 6%. So she was treated with recombinant FVIII and had an uneventful cesarean delivery under epidural anesthesia. After treatment, FVIII levels were 198%. The recombinant FVIII infusion was maintained postoperatively, but ten days after surgery she developed a brachial deep venous thrombosis.[253]

There are reports of bleeding in carriers of FVIII deficiency where the diagnosis was unknown. No information is given as to whether these women received regional or general anesthesia.[254] Acquired hemophilia can occur during pregnancy or postpartum due to an acquired inhibitor of FVIII. These women often present with severe bleeding. The aPTT is prolonged and is not corrected with addition of normal plasma. Remission usually occurs within a few months.[231] Treatment for severe bleeding is with FVIII concentrates (recombinant, monoclonal antibody purified products, or intermediate- and high-purity FVIII products).[249]

Table 17.5 Severity of hemophilia based on factor activity level

Level	Clinical severity	Clotting factor activity
Severe	Spontaneous musculoskeletal and internal bleeding	<1
Moderate	Occasional, spontaneous musculoskeletal bleeding	1–5
Mild	Delayed onset bleeding after trauma, surgery and dental extraction	5–35

Factor IX (FIX) deficiency (hemophilia B, Christmas disease)

This is an X-linked recessive bleeding disorder, which is indistinguishable from FVIII:C deficiency (hemophilia A) in clinical spectrum and heredity. Fifty percent of the sons of heterozygous maternal carriers are hemizygous and affected; 100% of daughters of affected men and 50% of daughters of carrier mothers are heterozygous carriers. As is seen in hemophilia A, women may be significantly affected due to extreme lyonization. However, unlike hemophilia A, FIX levels do not rise during pregnancy so pregnant carriers with low levels of FIX are at increased risk of bleeding peripartum.[255]

Five cases of FIX deficiency during pregnancy were reported in the obstetric literature up to 1991.[256] Four patients were followed throughout gestation with monthly FIX levels, and three of four had intrapartum plasma or FIX prophylaxis. The fourth patient presented at 28 weeks' gestation with thrombocytopenia and a retrochorionic hemorrhage. She was treated with FIX and eventually had a spontaneous vaginal delivery at 36 weeks' gestation. No mention is made of the anesthetic management.[256]

As FIX deficiency is an X-linked genetic disease, only 3% of the affected population are female. In a recent review of the obstetrical experience in women with FIX deficiency (two hemophilia B and three hemophilia B carriers), Yang and Ragni noted that four of the five had excessive postpartum bleeding during six of sixteen deliveries.[257] It was more common in those pregnancies where the women received fewer than four days of postpartum FIX replacement. There was no relationship between bleeding severity and the severity of FIX deficiency.

Although several cases of pregnancy in women with hemophilia B have been reported anesthetic management is not mentioned. As FIX levels do not increase during pregnancy, women with low levels prior to pregnancy should be considered at risk for hemorrhage peripartum. Regional anesthesia is contraindicated in women with low levels of FIX unless replacement therapy is given to normalize coagulation.

Factor X (FX) deficiency

Factor X is a vitamin K-dependent clotting factor and is the first enzyme in the common pathway of thrombus formation. It is synthesized in the liver, has a relatively long plasma half-life (40 hours), and is the most important activator of prothrombin. Severe FX deficiency (FX:C level <1 IU/dl) is inherited in an autosomal recessive manner and is estimated to have a prevalence of 1:1 000 000.[258] The heterozygous form has a prevalence of approximately 1:500 and heterozygous individuals are usually asymptomatic although some do have a bleeding tendency particularly when challenged. Homozygous individuals usually have severe bleeding that may manifest as epistaxis, hemarthrosis, or mucosal type bleeding. An individual with a FX:C level of 1–5 IU/dl may bleed only following surgery or trauma. There is prolonged PT and aPTT, which will correct when mixed with normal plasma unless an inhibitor is present.[16]

In pregnancy, FX levels generally rise to 163% of normal activity at 30 weeks, and return to normal six weeks postpartum. Administration of FX may be needed in pregnant women with severe disease or who have had a previous severe outcome.[16] Usually FX replacement is unneccesary if the FX:C >10 IU/dl or if there is a lower level with no bleeding history. A multidisciplinary approach is necessary to manage the pregnancy when both parents are known to have FX deficiency as there would be a significant risk of bleeding for the mother and baby.

Few cases of FX deficiency in pregnancy have been reported.[258,259,260,261,262,263] In one, the FX levels did not increase and the patient required FX concentrate due to placental abruption.[260] This patient eventually had an uneventful C/S with no mention made of anesthesia.

Factor XI (FXI) deficiency

This deficiency is transmitted as an autosomal recessive trait and is reported to occur in between 0.1% and 0.53% of Ashkenazi Jews.[16] There also is an increased frequency in families of Italian and German background. The prevalence of severe deficiency (FXI:C level <10 IU/dl) is estimated at 1:1 000 000. Unlike the classic hemophilias, the bleeding tendency does not correlate well with FXI and assessment of the patient's risk is best achieved through a detailed history and family history. Spontaneous hemorrhage is unusual and its occurrence may be dependent on other factor deficiencies. Factor XI deficiency has been associated with Noonan syndrome, Gaucher syndrome, VW disease, FVIII deficiency, and FVII deficiency. These patients may present with a prolonged aPTT and normal PT.

Factor XI levels normally decrease during pregnancy, in contrast to other factors which increase. At 28 weeks, FXI level is 81% and at term, 62% of nonpregnant levels. Depending on the level of FXI at term, these patients may require administration of the specific factor. Occasionally, these patients develop an inhibitor that may require anti-inhibitor complex to correct coagulation.[264] Replacement factors are only used in women with a clinical history of bleeding.

Patients with severe deficiency usually bleed during surgery. If the level is between 20 and 70 IU/dl, a bleeding history will indicate whether therapy is needed. Pregnancy carries the risk of PPH and bleeding at delivery and many advise administration of FXI concentrate to women with severe factor XI deficiency for C/S. In a report of women with severe FXI deficiency (<1 to 17 IU/dl) there were 139 vaginal deliveries (51 women), 13 C/S (six women), and five women had seven vaginal deliveries and five C/S.[265] The majority (43 women – 70%) did not experience a PPH during their 93 deliveries, and in those that had a PPH there was no relationship to FXI level or genotype. The authors recommend that FFP should be given only on demand in women with severe FXI deficiency during and after vaginal delivery, but they were unable to make a similar recommendation regarding C/S.[265]

Neuraxial anesthesia is contraindicated in women with FXI deficiency unless factor XI concentrate has been given with an adequate response. In one report of three women with FXI deficiency, all received neuraxial anesthesia.[266] In one, FXI deficiency was unknown prior to a PPH (FXI level 0.16 U/ml), in the second woman, the aPTT prior to an urgent C/S was prolonged (FXI level 0.26 U/ml). She was given two units of FFP with correction of the aPTT and she received a combined spinal–epidural anesthetic. The third woman was scheduled for repeat C/S and an aPTT was prolonged (FXI level 0.39 U/ml). She had an uneventful epidural for a previous C/S and so she had an epidural anesthetic, which was also uneventful.[266] In another report, a woman with FXI deficiency and an FXI inhibitor had general anesthesia for a C/S.[264]

Factor XII (FXII) deficiency

This is a rare disorder, which is transmitted in an autosomal recessive manner. Mild deficiency is estimated to occur in 1.5–3.0% in Caucasians[267] and some suggest that FXII deficiency is associated with thrombosis rather than bleeding. A recent report examining the occurrence of thrombosis suggests that a combination of severe FXII deficiency (homozygous) with other risk factors, such as pregnancy, surgery, trauma, and other thrombophilias, is more likely to be associated with thrombosis than Factor XII deficiency alone.[268] Factor XII deficiency does prolong the aPTT and has been associated with recurrent abortion.[267]

Factor XIII (FXIII) deficiency

The active form of FXIII is located mainly in platelets and monocytes. Activated FXIII crosslinks fibrin chains creating a stable thrombus that is more resistant to fibrinolysis. During pregnancy it is also present in the placenta.[269] Factor XIII is made up of two subunits, A and S, with the former having fibrin-stabilizing activity. Factor XIII deficiency can be inherited in an autosomal recessive manner or may be acquired. The frequency of deficiency is 1:1 000 000–2 000 000 with consanguinity often a common feature in affected families. Women with severe FXIII deficiency (FXIII:C level <1 U/dl) are at risk of spontaneous bleeding, while those with levels of 1–4 U/dl may have moderate to severe bleeding. Women with this deficiency have a history of severe bruising, muscle hematomas, hemarthroses, intracranial hemorrhage, spontaneous pregnancy loss, PPH, and bleeding after surgery or trauma. The PT and aPTT are normal.

During pregnancy, subunit S increases while subunit A tends to decrease causing a net reduction of FXIII that continues to decline. Although pregnancy loss is commonly reported, it is not inevitable and those with severe FXIII deficiency should receive FXIII concentrate when pregnancy is confirmed. Treatment should continue throughout pregnancy.[270]

Combined deficiencies

Combined FV and FVIII deficiency

This is a rare autosomal disorder that is often seen in situations of consanguinity. There are few data regarding the course in pregnancy. As FV does not consistently increase or decrease during pregnancy while FVIII level will increase, bleeding will most likely

be dependent on the FV level. In one report of five unrelated Indian families there were no cases of pregnancy.[271]

Vitamin K-dependent clotting factors inherited deficiency (VKCFD, Borgschulte-Grigsby deficiency)

There are few case reports of the autosomally recessive inherited combined deficiency of the vitamin K-dependent clotting factors. Individuals with this disorder experience a wide variation in bleeding tendency with presentation at various ages. There is a prolongation of PT and aPTT, which is dependent on the degree of reduction in activity of FII, FVII, FIX, and FX. Most individuals show some improvement with vitamin K therapy. Occasionally factor replacement is necessary. There is a single report of VKCFD during pregnancy that was managed with oral vitamin K.[272] Fresh frozen plasma was required for ongoing bleeding from an episiotomy.

Anesthetic management of patients with congenital coagulopathies

All patients with a diagnosis of a congenital coagulopathy benefit from an early consultation with a hematologist and anesthesiologist. This allows an assessment of specific factor levels, their response during pregnancy, and anticipated management for labor and delivery. If there is any question about coagulopathy, regional anesthesia is contraindicated.

Patients with VW disease are frequently denied regional anesthesia in spite of an improvement in their coagulation status during pregnancy, due to an increase in antihemophilic factor and VWF. Many respond to the use of DDAVP.[249] As VWF decreases rapidly postpartum it will be necessary to continue to monitor their coagulation status and possibly administer DDAVP in the postpartum period.

Regional anesthesia has been used successfully in patients with type I VW disease.[273,274,275] For C/S, spinal anesthesia may be preferred due to the smaller size of needle. However, as the levels of VWF decrease postpartum if epidural analgesia has been used, one should remove the epidural catheter promptly following delivery. There is one report of uneventful regional anesthesia in a parturient with type IIA disease following administration of Humate P.[276] Regional anesthesia was planned in a parturient with type IIB disease, but her platelet count remained low following administration of FVIII and platelets so general anesthesia was administered.[277]

Uniquely among the coagulation factors deficiency states, hemophilia A and B are inherited as X-linked recessive genes, but due to lyonization of the gene female carriers may exhibit coagulation abnormalities. Inwood and Meltzer[278] have pointed out the potential anesthetic problems. Balance the benefits versus risks of appropriate replacement therapy with the risks versus benefits of the anesthetic technique. Obviously, if there is an overt coagulopathy, regional anesthesia is contraindicated and an alternative technique should be used for labor analgesia. Normalization of factor levels to minimize bleeding risk prior to surgery will allow a broader spectrum of anesthetic options. In patients with a deficiency of FVIII:C, a good response to DDAVP can be anticipated and may normalize the FVIII:C level. This is safe therapy with none of the risks of factor concentrate. Consideration for factor replacement is based on the factor levels and their associated risk of delayed hemorrhage. These patients should be identified early in pregnancy and a consultation with an anesthesiologist and hematologist arranged so that management can be discussed. General anesthesia for C/S is the technique of choice if there is a coagulopathy.

Hypercoagulable states, heparin, and anesthesia

Pregnancy is defined as a hypercoagulable state and parturients are therefore at greater risk of thrombosis.[279] Parturients who have a hereditary predisposition to thrombosis (protein C, S, Z, or antithrombin III [ATIII] deficiency, or hereditary resistance to activated protein C [Factor V Leiden or prothrombin gene mutation G2010A]) or those who have antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody) are at even greater risk.[280] In addition to maternal risk there is increased risk of recurrent pregnancy loss, late fetal loss, preeclampsia, and abruptio placentae.[279,280] Most anesthesiologists are familiar with most of the thrombophilias but may not be aware that deficiency of protein Z, a cofactor for regulation of FXa activity, can also lead to pregnancy complications.[279]

Many pregnant women considered at high risk of thromboembolic disease, or with known thrombophilia resulting in fetal risk, are now treated with heparin prophylaxis.[279,281] Due to its lower complication rate and stable and predictable pharmacokinetics, LMWH may be the therapy of choice.[279,282] However, because of the potential risk of an epidural hematoma when regional anesthesia is administered concurrently with heparin, guidelines have been established as to the timing of regional anesthesia with respect to heparin (UFH, LMWH) administration.[159] Every obstetrical anesthesiologist should be familiar with these guidelines and follow them.

Maternal hydrops

Rarely, fetal and/or placental hydrops is accompanied by maternal hydrops.[283,284,285] This syndrome has variously been called Ballantyne syndrome, mirror syndrome (hydrops), triple edema, and pseudotoxemia. Isoimmunization (Rh disease, anti-Kell, anti-Duffy antibodies), infection (various viruses such as parvovirus), alpha thalassemia, sacrococcygeal teratoma, aneurysm of the vein of Galen in the fetus, and placental tumors have been implicated as the origin of hydrops in the fetus and placenta. The etiology of maternal hydrops is unknown.

Clinically there are similarities to preeclampsia with massive edema, mild or moderate proteinuria, and mild hypertension, hence the name pseudotoxemia. However, other well-documented cases have no proteinuria or hypertension. Generally the edema is severe, mainly involving the extremities. Clinically, the patient may complain of shortness of breath due to pulmonary edema and/or polyhydramnios with upward pressure on the diaphragm

and/or ascites. There may be associated anemia and elevated plasma uric acid. In some early reports, Rh isoimmunization was diagnosed on the basis of severe edema in the mother.

Mirror syndrome is associated with a high incidence of perinatal mortality because of fetal hydrops. Delivery of fetus and placenta often leads to rapid devolution of the maternal syndrome. Until such time as delivery occurs maternal morbidity secondary to pulmonary edema and renal failure can be significant.

Anesthetic involvement with these patients may include provision of analgesia for labor, resuscitation measures, and insertion of arterial and central catheters. If epidural analgesia is used, a cautious approach to fluid loading and slow incremental injection of local anesthetic are important.

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18 INFECTIOUS DISEASES IN PREGNANCY

Gabriela Rocha Lauretti and Robert S. F. McKay

Bacterial infections

Clinical features: fever and asymptomatic patient

Fever during pregnancy can result from a variety of infections, tissue trauma, malignancy, epidural analgesia, drug administration, and endocrine or immunologic disorders. Infection is the most common cause, reflecting the effect of pyrogens on the hypothalamus.[1] Bacterial infections of the skin, periodontal tissues, respiratory and genitourinary tracts can lead to pregnancy-related complications such as preterm labor, premature rupture of membranes, abortion following pelvic inflammatory disease, chorioamnionitis, neonatal infections, cervicitis, urethritis, ectopic pregnancy, low birthweight, stillbirth, pneumonia, septicemia,[2,3] and both maternal and neonatal death. Urinary tract bacterial infections usually arise from preexisting covert bacteriuria and experts recommend screening and eradication of these silent infections as routine prenatal practice.[4] Antibiotic treatment during pregnancy is beneficial in reducing neonatal and maternal morbidity/mortality, and most bacterial infections are preventable and treatable.[4,5,6,7,8] Clindamycin in early pregnancy can reduce the risk of preterm birth by 40–60%.[2] Vaginal bacterial diseases are often asymptomatic and have little impact on management by the obstetric anesthesiologist. The more common bacterial infections and related complications are listed in Table 18.1.

Maternal and fetal implications

The incidence of maternal infection during labor has been estimated to be about 3%.[22] Severe sepsis is less common, however, and presents as the primary problem in $< 1\%$ of patients.[23] However, sepsis remains a significant cause of maternal death in underdeveloped countries.[24] In pregnancy, there are decreases in immunoglobulin G levels, lymphocyte count, and impaired lymphocyte activity. Further, a change in the balance of Th1/Th2-type cytokines favors T helper type 2 immunity,[25] and leads to an increase in asymmetric antibodies.[26] Although these changes promote maternal tolerance of the fetus, they also may place the parturient at added risk for infection.

Maternal complications of sepsis include pneumonia, adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), pulmonary edema, septic pulmonary emboli, septic shock, decreased left ventricular function, and cardiac arrest. Five percent of septic shock cases in the obstetric population are caused by gram-positive bacteria and 95% by gram-negative organisms.[18] The diagnosis is made by attention to the history, physical examination, and laboratory findings (see Table 18.2).

It is uncertain if the preterm fetus can develop an inflammatory response and modulate inflammation to prevent injury. Fetal exposure to inflammation can induce lung maturation. The fetus at risk of early preterm delivery may be exposed to chorioamnionitis and glucocorticoids. This may increase or decrease fetal inflammatory response, depending on when exposure occurs. The immunomodulatory capacity of the fetus remains unexplored.

An increased risk of septicemia and puerperal fever in women undergoing cesarean section (C/S) is one reason why vaginal delivery is the preferred delivery mode for healthy women.

Anesthetic management of the septicemic parturient

Anesthesia with concurrent sepsis involves serious physiological stress upon multiple organ systems. However, pregnant patients may be protected during sepsis by oxytocin, which limits sepsis-induced oxidative damage by acting as an antioxidant agent. Oxytocin has a protective effect on the colon and liver that may be dependent on its inhibitory effect on neutrophil infiltration, limiting sepsis-associated multiple organ damage.[29] The clinical importance of oxytocin in this regard is unknown. Correction of perioperative hypothermia may improve survival after sepsis by modulating early inflammatory responses.[30]

When anesthetizing a septic parturient, assess intravascular volume, to include invasive monitoring in severe cases. Antibiotic therapy should be initiated before any anesthetic intervention. The need for emergency C/S must be weighed against the need for preoperative fluid resuscitation of the mother. Infection in pregnancy raises questions about the safety of regional anesthesia in febrile patients. Despite this concern and a lack of guidelines, the presence of infection and fever in labor is not an absolute contraindication to regional anesthesia. Indeed, epidural analgesia has been associated with improved neonatal acid-base status,[31] and, in endotoxemic rats, produces better redistribution of organ blood flow.[32] However, inducing epidural anesthesia in the presence of sepsis remains controversial. Sympathetic block induced by neuraxial anesthesia may be disastrous in a septic, hypovolemic parturient. Epidural anesthesia titrated for labor or nonurgent C/S is acceptable if intravascular volume has been optimized. Epidural anesthesia has been associated with a slightly longer labor,[33] which may contribute to maternal fever.[34] Although fever associated with epidurals is unlikely to adversely affect the fetus, epidural analgesia has been associated with increased rates of neonatal sepsis evaluation in some institutions.[35] Hence, criteria for these evaluations need to be adjusted in the presence of epidural anesthesia.

For emergency C/S, use a rapid-sequence general anesthetic induced with intravenous (i.v.) ketamine 1–2 mg/kg and succinylcholine 1 mg/kg, and, if required, concomitant fluid resuscitation

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Table 18.1 Bacterial infections

Etiological agent	Related complications of interest
Bacterial vaginosis (*Gardnerella vaginalis, Ureaplasma urealyticum, Mycoplasma hominis, Mobiluncus species, Bacteroides bivius*)	Complex vaginal infection; increased susceptibility during pregnancy;[9] incidence of endometritis after C/S varies from 3–95%, even in patients receiving prophylactic antibiotics.
Neisseria gonorrhoeae	Increased in women with lowered immunity, commonly associated with HIV; increased in women on birth control pills; rarely may lead to systemic sepsis, endocarditis, and/or arthritis; pharyngitis from oral sex is possible; alters the inflammatory responses elicited in human infection.[10]
Chlamydia species	Three species of the genus *Chlamydia* are pathogenic in humans and cause pneumonia. *C. pneumoniae* leads to pneumonia in adults and may be associated with intrauterine growth restriction (IUGR) and peripartum cardiomyopathy. *C. psittaci* is a tropical disease and is discussed later in the chapter with other tropical infections. *C. trachomatis* is the most commonly reported sexually transmitted disease in the United States. It causes infection of the maternal birth canal and can ascend to cause neonatal conjunctivitis and blindness, naso-pharyngitis, otitis media, and pneumonitis. *C. trachomatis* infection is associated with premature delivery, spontaneous abortion, stillbirth, and ectopic pregnancy. The organism is common among pregnant women with an estimated prevalence of 5–22%. Therefore, it is recommended that all women under the age of 25, and those at increased risk of infection (e.g. multiple sexual partners) be screened and treated.[11] The vertical transmission rate of *C. trachomatis* is estimated to be 55%.[12] Untreated infection of the neonate may lead to pneumonia and prolonged apneic spells. Eyrthromycin is the treatment of choice. Azithromycin is an alternative therapy and has been shown to be safe in pregnancy and more efficacious than erythromycin.[13,14] Eradication of *C. trachomatis* should include treatment of the mother and her sexual partner. Vaccines against Chlamydia are being researched currently.
Listeria monocytogenes[15]	Mother: usually a mild flu-like (abdominal pain) illness, CNS symptoms (if meningitis occurs). Infant: sepsis, pneumonia. Macroabscesses in the placenta.
Treponema pallidum	Clinical manifestations depend on chronologic state of the disease, the second phase associated with splenomegaly, lymphadenopathy, and widespread mucocutaneous lesions; tertiary phase characterized by cardiovascular and central and peripheral nervous systems lesions; linked to low socioeconomic standards; perinatal mortality = 60/1000 deliveries of newborns > 1000 g.[16] Recent increase in incidence has occurred in homosexual men.[17]
Streptococcus species (Group A beta-hemolytic; Group B streptococci)	*Group A*: symptomatology varies from mild influenza-like illness to tachypnea/cyanosis with poor peripheral circulation. Cases of puerperal sepsis; postpartum meningitis and maternal death have been reported following epidural anesthesia. *Group B*: postpartum meningitis; bimanual examination of the parturient prior to rupture of membranes may lead to invasion of blood stream by unsuspected vaginal Group B *streptococci*, leading to meningitis before onset of labor. NSAIDs may induce progression of streptococcal (A and B) infections to toxic shock syndrome.[5]
Escherichia coli	Association between bacteriuria and pyelonephritis in pregnancy, hypertension, preeclampsia, anemia;[18] predisposition to ulcerative colitis? (elevated urinary antibodies to *E. coli*).
Staphylococcus species (*S. aureus, S. hemolyticus, S. epidermidis*)	Vertical transmission, extradural abscess formation may be related to extradural analgesia; sepsis with multiorgan system involvement; if associated with ARDS in pregnancy, extracorporeal carbon dioxide removal may be life saving. Relationship between the use of NSAIDs and the progression of staphylococcal infections to toxic shock syndrome?[19]
Campylobacter species	Bacteremia, Guillain-Barré syndrome, and reactive arthritis are the most serious of the long-term consequences of *C. jejuni* infection. Diarrhea leading to maternal dehydration and electrolyte disturbances; 90% prematurity, 80% neonatal mortality rate.[20]
Actinomycosis israeli	Right flank pain, infection may be clinically confused with appendicitis.
Pertussis species	The incidence has risen in recent years; highly contagious respiratory disease, infected adolescents and adults with mild illness are source of potentially life-threatening illness in infants and young children. Acellular pertussis vaccines are recommended for entire primary vaccination series.[21]
Clostridium botulinum	Anerobe producing potent food-related toxin; maternal GI upset, dehydration, lethargy, slurred speech, muscle weakness, ↓ FRC; preterm labor, abruption; toxin does not cross placenta.

HIV = human immunodeficiency virus; CNS = central nervous system; g = grams; GI = gastrointestinal; FRC = functional residual capacity; ARDS = adult respiratory distress syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs

Table 18.2 Maternal sepsis

Risk factors	Previous history of recent upper respiratory or urinary tract infection, premature rupture of membranes;[18,27] >24 hours prolonged fasting;[18] bimanual examination of parturient with asymptomatic bacteruria prior to rupture of membranes.
Clinical findings[a]	Minor: increased fetal tachycardia, shivering, hyperthermia, meconium-stained amniotic fluid, dystocia;[18] Absolute: body temperature >38 °C or <36 °C, a white blood cell count >12 000 cells/mm^3, <4 000 cells/mm^3 or >10% immature (band) forms.[27] Metabolic acidosis, altered mental status, and oliguria are all signs of hypoperfusion and severe sepsis.
Procedures	Continuous fetal heart monitoring; fetal scalp pH sampling. Extracorporeal carbon dioxide removal combined with low-frequency positive pressure ventilation may be life saving for ARDS unresponsive to traditional therapy (PaO_2 <50 mmHg on 100% oxygen).[28]

[a] At least two minor clinical findings must be present in the absence of any risk factors for 95% confidence interval to diagnose sepsis.[18]

and antibiotic therapy. Since sepsis is associated with a high risk of progression to acute lung injury or ARDS, careful evaluation should be made prior to extubation of the trachea. Ketamine has been advocated for anesthesia in septic patients because it is a cardiovascular stimulant. However, if endogenous catecholamine stores are exhausted, ketamine may act as a cardiodepressant. Ketamine attenuates liver injury from endotoxemia by reducing cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS).[36] However, it takes supra-anesthetic doses of ketamine to inhibit endotoxin-induced pulmonary inflammation in vivo.[37] Etomidate is another potential anesthetic induction agent in sepsis since it maintains cardiac function, but it has the potential to impact negatively corticosteroid production. Since severe sepsis is associated with relative adrenal insufficiency, etomidate may not be the best option. Propofol is not indicated in these women as it causes dose-dependent hypotension, particularly with intravascular volume depletion. The use of desflurane during septic shock has been reported.[38] Maintenance of anesthesia with an infusion of i.v. ketamine (2–4 mg/kg/h) and O_2/N_2O is one option. Prophylactic treatment with nitric oxide donors regulates systemic inflammatory response and minimizes renal damage in experimental models.[39]

Viral infections (see Appendix to Chapter 18 for viral classification)

Viral infections in pregnancy are of concern to the obstetric anesthesiologist. Viruses of clinical interest include human immunodeficiency virus (HIV), hepatitis viruses, herpes simplex viruses, cytomegaloviruses, papillomaviruses, parvoviruses, and the viruses that cause chickenpox, measles, influenza, and rubella. Maternal viral infection is associated with an increased risk for adverse perinatal outcome. The acronym TORCH is frequently applied to agents known to cause serious congenital infections. Except for *Toxoplasma gondii*, all TORCH agents are viruses: rubella, cytomegalovirus, herpes simplex, varicella zoster, and HIV.

Use standard precautions by wearing gloves, using eye protection, and taking care when handling blood and body fluids.

Human immunodeficiency virus

HIV/acquired immunodeficiency syndrome (AIDS): epidemiology and implications for the obstetric anesthesiologist

Human immunodeficiency virus (HIV disease or AIDS) is the greatest health crisis of the twentieth and early twenty-first century. For example, HIV/AIDS-associated disease was the leading cause of mortality at the Johannesburg Hospital, South Africa, in 2000/2001 (42.7%, increasing from 20% in 1995/1996) with pneumonia the commonest cause of death.[40] AIDS is also a major cause of death in the USA where, as of December 2004, 944 306 persons had a diagnosis of AIDS and 529 113 (56%) died.[41] AIDS is a multiorgan disease that has broad implications for anesthesiologists, requiring an increasing amount of care. Risk factors include: homosexuality, i.v. drug use, sex with an i.v. drug abuser, crack cocaine use, blood transfusion, sexually transmitted disease, multiple sexual partners, and tattoo of body surfaces.

Screening women with risk factors detects about one-half of those who are HIV-seropositive, but if screening is applied to all pregnant women the rate increases to 87%.[42] These data, among others, led the Centers for Disease Control (CDC) in 2006 to change its recommendation to advocate routine voluntary HIV screening as a normal part of medical practice in the preconception period or in early pregnancy. A second screening test should also be recommended in the third trimester. If a high-risk woman with undocumented HIV status presents for labor, then a rapid test can be performed. Women have the option to decline testing (opt-out screening).[41] The enzyme-linked immunoabsorbant assay (ELISA) and the Western Blot remain the main tests for the initial diagnosis of HIV infection. Measures of CD4+ T-lymphocytes are used to guide clinical and therapeutic management of HIV-infected individuals.[42]

Primary care for HIV-infected patients includes ensuring that eligible patients receive hepatitis B and A virus vaccinations, that all women undergo appropriate screening and follow-up for cervical cytologic abnormalities, and screening for renal function abnormalities.

HIV impact on pregnancy and the fetus

Ninety percent of children infected with HIV contract the virus from their mother while in utero, during delivery, or postpartum. Worldwide, mother-to-child transmission of HIV-1 is estimated to be responsible for 1800 new infections in children daily.

Antiretroviral therapy significantly reduces the risk of transmission. When highly active antiretroviral therapy (HAART) is used, mother-to-child transmission rates are reduced to $<2\%$, in the absence of breastfeeding.[43] In the USA the number of children with AIDS from perinatal HIV transmission peaked at 945 in 1992 but declined by 95% in 2004.[41] Asymptomatic HIV positive women with a CD4+ count below 500/mm^3 or p24 antigenemia were found to be ten times more likely to transmit the virus to their offspring.[44] The presence of a low CD4+ lymphocyte count early in pregnancy may help women decide whether to discontinue the pregnancy.

Breastfeeding significantly increases the risk of HIV transmission. Breastfeeding adds a 12–26% risk of vertical infection over and above the risk of transmission at delivery or in utero. In one study, up to 35% of all HIV-infected children had been infected through breastfeeding.[45] Risk factors for HIV transmission by breastfeeding include acquiring HIV postpartum while breastfeeding (29% risk of transmission vs. 10% risk if infected before pregnancy); degree of maternal plasma and breast milk viral load; and the presence of mastitis.[45] As a result, HIV-infected women are advised against breastfeeding. Possible solutions to allow breastfeeding include use of antiretroviral therapy and treatment of the infected milk.[46] It is uncertain if maternal HIV infection increases adverse perinatal outcomes, such as preterm labor. A neonatal evaluation at 12 months of age is required to be certain of the HIV status of a child born to a HIV positive mother.[47]

HIV-infected babies have the same frequency of congenital abnormalities as those not infected and there is no consistent pattern of defects. This suggests that viral transmission occurs late in pregnancy or at the time of delivery.[48] Precautions to reduce the risk of transmission include removal of all maternal blood and fluids immediately after delivery, avoiding percutaneous umbilical cord sampling and fetal-scalp electrodes, and avoiding vacuum or forceps delivery.

Cesarean section versus normal vaginal delivery

Although C/S produces higher rates of septicemia and puerperal fever compared with vaginal delivery, a C/S in the HIV parturient has the advantage of reducing the time of contact between maternal blood and the neonate. Indeed, a Cochrane review concluded that elective C/S is an efficacious intervention for prevention of mother-to-child transmission of HIV-1 in those not taking antiretroviral drugs or just taking zidovudine.[49] However, if C/S is performed once labor has started then it confers no protective effect against intrapartum transmission of HIV-1. There is little evidence to suggest that HIV or antiretroviral drugs increase the rate of pregnancy complications or that pregnancy alters the course of HIV infection. Isolation of HIV-1 from cervical secretions of women at risk has been described previously.[50] The cervical mucus plug has antimicrobial properties and represents a physical/chemical barrier against bacterial (and viral?) invasion.[51] Rupture of membranes for $\geq$4 hours is also another risk factor.[52] The risk of infection in the first-born twin is 2.8-fold greater than that of the second,[53] possibly as a result of a prolonged contact with maternal blood.

Regional versus general anesthesia: anesthetic considerations

Human immunodeficiency virus infection should not contraindicate regional anesthesia, as there is no direct evidence that lumbar puncture facilitates central nervous system (CNS) disease by introducing virus from blood into the cerebrospinal fluid (CSF). In addition, HIV has low infectivity. General anesthesia (GA) is safe, but drug interactions and their impact on various organ systems should be considered. Regional anesthesia is often the technique of choice. Nevertheless, one must take into consideration the presence of neuropathies, local infection, or blood clotting abnormalities. Sensory neuropathy, manifest by painful dysesthesias, especially in the feet, is common, occuring in 10% to 30% of AIDS patients.[54] This poses a challenge for the anesthesiologist presented with an AIDS patient without a central or peripheral neuropathy.[55] The appearance of neurologic symptoms shortly after delivery could represent natural evolution of the disease or an anesthetic complication. Among asymptomatic HIV-positive individuals, 40–60% have positive CSF markers for viral infection, indicating early involvement of the CNS.[55,56] Some suggest avoiding GA in AIDS patients if a regional technique is possible because of depressed immunity.[57] If GA is used, HIV patients with CNS disease may be more sensitive to psychoactive drugs such as benzodiazepines, opioids, and neuroleptics. This sensitivity may be due to the interaction between interleukin-1 (a cytokine with sedative effects released in the acute phase reaction to viral or bacterial infection) and the γ-aminobutyric acid-A (GABA-A) receptor.[58] Thus, AIDS patients may be more sensitive to GABAergic drugs such as barbiturates, benzodiazepines, and propofol during the acute viral phase. If etomidate is used, early neonatal feeding is recommended in order to avoid neonatal hypoglycemia. Etomidate has a transient depressant effect on fetal plasma cortisol levels, especially those subjected to intrauterine stress. Onset time and duration of vecuronium in AIDS patients may be prolonged compared to noninfected controls[59] because of peripheral neuropathy[60] and the effects of zidovudine[61] and didanosine.[62] AIDS patients may suffer more frequent neuroleptic-induced extrapyramidal signs after physostigmine, droperidol, or carbamazepine. The latter should all be used in lower doses. Halothane and isoflurane inhibit interferon-α/β (INF-α/β) inducible cytotoxicity related to natural killer (NK) cells. The loss of sensitivity of NK cells to stimulation by INF-α/β could be expected to compromise the NK cell effectiveness in postanesthetic immune responses. Interestingly, NK activity already enhanced by IFN-α/β before exposure to anesthetics is not affected by anesthesia.[63] Opioids may reactivate latent CNS HIV infection.[64] Morphine has been shown to reactivate or stimulate HIV reproduction in vitro.[65] Morphine potentiates apoptosis within human fetal neuronal cell cultures[66] and attenuates the antiHIV activity of T cells in HIV latently infected cells.[67] In vivo animal models have shown a suppression of humoral and cell-mediated immune responses by opioid agonists through direct[68] and indirect mechanisms.[64] Some studies demonstrating viral reactivation[64] or opioid immune supression[68] were in patients who required chronic opioid use. Despite these studies, short-acting opioids may be the analgesic choice in balanced GA.

Further studies are required to predict the overall perioperative risk for the HIV-positive patient.

Conclusions

In the absence of intracranial hypertension and coagulopathy, neuraxial anesthesia is recommended for surgical procedures in parturients with AIDS, independent of gestational age. However, the mother should have the risks and benefits of a general versus regional anesthetic technique explained, and she must participate in the decision-making process. The use of neuraxial opioids in patients with HIV has not been fully studied.

Viral hepatitis (see also Chapter 14)

Acute viral hepatitis is the most common cause of jaundice in pregnancy. The course of most viral hepatitis infections (hepatitis A, B, C, and D) is unaffected by pregnancy. A more severe course of viral hepatitis in pregnancy is seen with hepatitis E.[69] For further details see Chapter 14.

Herpes simplex viruses (HSV)

Herpes infection occurs in approximately 1 in 7500 births in the United States.[70] Most patients with HSV-2 antibodies have no historical, clinical, or virological evidence for HSV-2 infection. They are identified as HSV-2 carriers on the basis of HSV-2 antibody screening. Herpes simplex virus-1 has been isolated from the genitourinary tract or anal canal in 3.5% of women with HSV-1 antibodies,[71] and of these 66% were symptomatic. In Europe, clinically probable genital herpes was observed in 25% of subjects with HSV-2 infection and in some subjects with HSV-1 infection. Coinfection with HSV-1 appeared to protect against symptom expression in those infected with HSV-2.[72]

In primary HSV infection, dysuria is the most common complaint (80% of patients). In one study, 70% had vulvar ulceration, 66% had tender inguinal lymph nodes, and 46% had a cervical ulcer. Of those with recurrent genital infection, two-thirds had vulvar ulcers.[73] Serologic tests for HSV-2 are reliable for detecting recurrent genital infections, while culture is the most effective diagnostic technique for primary infections.[73]

Women with asymptomatic or unrecognized HSV-2 infection are at risk of delivering babies who develop neonatal herpes. Neonatal herpes infection is associated with significant morbidity and mortality, despite antiviral therapy.[71] Most fetal complications result from ascending infection after rupture of membranes or passage of the neonate through an infected birth canal. If lesions are present at the time of delivery then C/S is recommended.[74]

General, epidural, and spinal anesthesia have all been used safely in women with active recurrent herpes simplex lesions. Although concerns exist about introducing virus into the CNS during primary infection, only one report of transient postpartum neurologic deficit in association with regional anesthesia and primary infection has been published.[75] Nonetheless, some caution against the use of regional anesthesia during primary infection because herpes simplex encephalitis is such a devastating infection. Indeed, despite antiviral therapy, two-thirds of survivors have significant residual neurologic deficits.[76] Herpes encephalitis is part of the differential diagnosis of seizures during pregnancy.[77] One report describes the failure of acyclovir to prevent neonatal infection in a parturient with herpes type 2 encephalitis.[78]

There is evidence of HSV-1 reactivation in patients after the use of epidural morphine,[79] epidural fentanyl,[80] and intrathecal morphine.[81] The mechanism is unclear, but opioid activity within the spinal nuclei of the trigeminal nerve may be responsible.[79]

Cytomegalovirus

Cytomegalovirus (CMV) seroprevalence among women of childbearing age ranges from 30–100%.[82] Its incidence in the lower genital tract has been reported to be from 4–12%,[83] and CMV is the major pathogen detected in cases of placental infection associated with fetal death.[84] Clinical manifestations of virus replication are seldom seen, except in immunocompromised individuals. Following primary infection, the virus can be isolated from urine for months to years, with a greater risk of neonatal infection among mothers who continue to shed virus.

Congenital CMV infection is the leading cause of mental retardation and hearing impairment. Following primary CMV infection, the rate of transmission to the fetus is about 40%. More than 90% of the approximately 40 000 infants with congenital CMV infection born in the USA each year appear normal at birth.[85] Cytomegalovirus recurrence during pregnancy appears to be mainly due to reactivation rather than reinfection. However, in low-income nonwhite women a high proportion of congenital CMV infection is due to recent maternal infection and not reactivation of infection.[86] Maternal humoral immunity may not protect the fetus, which can become infected after recurrent and primary maternal infection. There is a high incidence of CMV reactivation in mothers during lactation, and a significant risk of transmission to preterm infants through breast feeding.[87]

To date, there is no effective intervention for primary CMV during pregnancy, but in one study hyperimmune globulin therapy was found to be safe and it produced a significant reduction in congenital CMV infection.[88] Controlled studies are required to confirm this benefit. Elective C/S is recommended for infected individuals since cervical contamination is usually responsible for neonatal infection.[85] However, since placental infection occurs in 4% of women with CMV,[84] C/S will not prevent all cases of neonatal CMV. The primary means of prevention of CMV is avoidance of infection during pregnancy through good personal hygiene.

There are no special anesthetic considerations for the parturient with CMV infection. It should be kept in mind, however, that immunocompromised patients with CMV may develop fulminant hepatitis or significant neurologic disease including myelitis.[89]

Human papillomavirus

Human papillomavirus (HPV) is a very common sexually transmitted infection in the USA and sexually active adolescents are at

high risk. There are over 100 serologic types of HPV and > 99.7% of cervical cancers contain at least one high-risk type, with approximately 70% containing types 16 and 18.[90] Vaccines are available for various serotypes of HPV, with the initial targets being types 16 and 18, and types 6 and 11.[91] It is hoped that widespread use of these vaccines will significantly reduce future morbidity and mortality from carcinoma of the cervix.

Human papillomavirus 6 and 11 infections are responsible for 90% of genital warts and nearly all recurrent respiratory papillomatosis, but are considered low risk and unlikely to be involved in cervical cancer. Most HPV infections become undetectable within one to two years, perhaps as a result of type-specific acquired immunity. Multiparity, oral contraceptives, and smoking are risk factors for persistence and progression of the disease. This reflects an increased expression of the virus as a consequence of hormonal depression of the immune system.

Condyloma from HPV infection begin as small, verrucose growths, usually on the vulva or genital area. Dysplasia is usual. There is a marked tendency for the lesions to become more prominent during pregnancy and to coalesce into cauliflower-like or raspberry-like masses. These are occasionally so extensive as to cause obstruction of the birth canal.[92]

Massive vulvar lesions may expose the parturient to lacerations, sepsis, and significant bleeding during vaginal delivery so elective C/S may be preferable. An association between maternal condyloma accuminatum and neonatal laryngeal papillomatosis is controversial.[93] Neonatal infection may occur transplacentally, but there may be greater risk of transmission from vaginal delivery. Prolonged labor is associated with a two-fold greater risk of disease transmission.[94]

Laser treatment of HPV produces a plume that can contain infective particles,[95] so surgical smoke should be evacuated and all personnel attending laser therapy should wear special face masks and eye protection.

Varicella-zoster virus (chickenpox)

Varicella-zoster virus (VZV) is highly contagious with secondary attack rates of 80–90% and seroprevalence rates > 90%.[96] Approximately 7000 pregnancies annually are complicated by varicella,[97] while about 6000 pregnant women annually have herpes zoster.[98] The average incubation period is 14 days. It occurs more frequently during late winter and early spring. A day after onset of fever, a nonsynchronous maculopapular rash appears on the skin and mucosa. The lesions undergo vesiculation and appear as pruritic, superficial thin-walled vesicles, arising in crops.

The incidence of VZV is no higher in pregnant than in nonpregnant women. Varicella-zoster virus primary infection, or chickenpox, during pregnancy appears to be associated with increased maternal morbidity and mortality. Pregnant women are more likely to develop hypoglycemia, pneumonia, encephalitis, hepatitis, pancreatitis, and nephritis after chickenpox infection. Most cases of varicella pneumonia in pregnancy occur in the third trimester. In one report of 17 cases of varicella pneumonia during pregnancy, the mortality rate was 41% compared to 17% in nonpregnant varicella pneumonia.[99] In-utero infection can produce congenital varicella syndrome, postnatal herpes zoster without a history of chickenpox in an infant, or positive immunity without clinical signs.[100] Maternal viremia leads to transplacental infection of the fetus in 25% of cases. Congenital varicella syndrome occurs when the fetus is infected during the first half of pregnancy. Affected newborns are likely to have intrauterine growth restriction (IUGR) and skin changes, e.g. hypertrophy, erythema, and scar formation (cicatrix). They may also have brain malformations (e.g. cortical atrophy and dilated ventricles), hypoplastic limbs, and an array of other defects, depending on the timing of infection in relation to organogenesis. Congenital varicella syndrome occurs in 0.4–2.0% of infected mothers.[101] Varicella-zoster immune globulin is given to exposed VZV-seronegative pregnant patients. Those women with a past history of chickenpox or positive VZV serology are considered to be immune. With the introduction of the varicella vaccine, the rate of varicella in pregnancy is expected to decrease dramatically. Pregnancy should be avoided within one month of varicella vaccine and the vaccine should not be given during an existing pregnancy.[102]

Spinal anesthesia for C/S in a woman with varicella has been described.[102] The woman was noted to have active lesions, fever, and a productive cough at 39 weeks' gestation. She was given varicella immunoglobulin and surgery was deferred for nine days at which time she was afebrile and the lesions were dry and crusted. An uneventful spinal anesthetic was performed in an area of skin free of lesions. Her fetus had congenital disease and was treated with acyclovir.

The CNS is the most common site for extracutaneous involvement with varicella and CNS infection can lead to acute cerebellar ataxia, encephalitis, meningitis, or Guillain-Barré syndrome. Brown and colleagues speculated that a pencil-point spinal needle would be less likely than an epidural needle to core tissue and introduce infected cells into the neuraxis.[102] They recommended that GA be used when active lesions are present. Before antiviral therapy, 65% of pregnant women with varicella developed varicella pneumonia – the current rate is <10%. High death rates have been observed with varicella pneumonia during pregnancy,[99] but a recent series of 18 women with varicella pneumonia reported no maternal deaths.[103] This suggests that antiviral therapy is effective (e.g. acyclovir 7–10 mg/kg i.v. three times a day for seven days).[103] Although prior VZV infection is thought to confer immunity, exposure of medical personnel (and others) to infectious patients should be avoided or minimized since secondary infections are more common than previously thought.[102]

Rubeola (measles)

Measles is a highly contagious exanthematous viral illness caused by a paramyxovirus (*Morbillivirus*). Its incidence worldwide has decreased dramatically since the introduction of effective vaccines, nevertheless, outbreaks still occur among clusters of individuals, especially young adults that vaccination programs have failed to reach. In 1997, it was estimated that 50 million cases occur annually worldwide with 1 million deaths.[104]

Although substantial progress has been made worldwide in vaccination programs, measles still remains the fifth leading cause of mortality among children under five years of age.[105] Susceptible young women are at unique risk because measles in pregnancy follows a more complicated course than in nonpregnant women.

Measles in pregnancy is defined as an illness in a pregnant woman meeting the definition for "probable measles" by the CDC. This clinical definition includes generalized rash, which occurs simultaneously with the onset of the effector phase of the antiviral immune response, cough, coryza, conjunctivitis, and temperature greater than 101°F during three or more days. Antibody status can be determined by ELISA. A retrospective study of 58 women with measles during pregnancy revealed that pregnant women were nearly twice as likely to be admitted to a hospital, nearly three times as likely to be diagnosed with pneumonia, and more than six times as likely to die from measles' complications.[106] In a study of eight infected pregnant women,[107] three of the four cases that presented before 24 weeks' gestation ended in abrupt spontaneous abortion or stillbirth. In contrast, the four pregnancies that presented after 25 weeks' gestation ended in live term deliveries, but two of the four neonates had congenital measles.[107]

Susceptible pregnant women exposed to measles should receive immunoglobulin within six days of exposure. Infants born to infected mothers should also receive immunoglobulin. Maternal HIV infection may reduce levels of measles antibodies in newborns, and low levels of measles antibodies at birth render children susceptible to measles infection at an early age. A combination measles, mumps, rubella, and varicella vaccine that produces nearly 100% seropositive conversion is now available. Vaccination is contraindicated during pregnancy and nonpregnant women receiving rubeola vaccination should use effective contraception for three months after inoculation.[108]

Influenza virus

Influenza is highly contagious and a major cause of respiratory disease in adults. Pregnant women do not get influenza pneumonia more often than nonpregnant women, but it can result in greater morbidity and mortality. Yearly immunization is recommended, and during the "flu season" influenza vaccine is recommended for all pregnant women in their second or third trimester. Fetal exposure to influenza infection two to four months prior to birth may be a risk factor for developing schizophrenia in adult life.[109]

China is an epicenter for the emergence of pandemic influenza viruses. However, the intensification of the poultry industry worldwide, coupled with the spread of viruses such as the Eurasian lineage of H9N2, suggests that a pandemic could take place elsewhere in the world. Although the highly pathogenic avian influenza virus H5N1 has produced little human disease to date, its evolution over time is concerning.[110]

Parvovirus B19 (Fifth disease)

Parvovirus B19, the causative agent of Fifth disease, is associated with hydrops fetalis. Approximately 35–50% of the general population is susceptible to the virus, while 20% will become infected after exposure.[111] Approximately 1–5% of pregnant women will be affected, with most having a normal outcome.[112] The risk of fetal death from placental transmission of parvovirus ranges from 1% to 15%,[113] with an increase in adverse outcomes when maternal infection occurs in the first two trimesters. Maternal symptoms include malaise, low-grade fever, maculopapular rash ("slapped cheeks"), and a symmetric polyarthralgia involving the hands, wrists, and knees that resolves spontaneously. Maternal symptoms do not correlate with the presence or severity of fetal infection. The fetus can be normal or suffer from aplastic anemia, myocarditis, nonimmunologic hydrops, and increased perinatal mortality. Ultrasonographic signs of fetal infection include ascites, pleural or pericardial effusions, skin edema, polyhydramnios, cardiomegaly, placentomegaly, and decreased fetal movement.[114] Maternal serum α-fetoprotein elevation may be the result of hepatic or placental damage and predicts poor fetal outcome.[115] Treatments have included fetal transfusion,[116] digitalization,[117] serial thoracocentesis, or paracentesis. There is no parvovirus vaccine for humans currently.

Rubella (German measles)

Rubella is a self-limiting low-risk maternal viral infection[119] that has the potential to cause serious fetal disease including the congenital rubella syndrome (CRS). It is caused by a togavirus of the genus *Rubivirus*. Some recommend a review of the rubella vaccination recommendations because most healthcare providers are seronegative.[120] Rubella is unlikely to be acquired as a result of casual or brief contact. Seronegative patients are at greater risk of acquiring infection when they have been exposed more closely over a long period. Maternal postauricular adenopathy may be detectable a week prior to development of a characteristic maculopapular rash and may persist for one to two weeks after disappearance of the rash. A high incidence of arthritis among young women has been described.[121]

Congenital rubella syndrome will occur in infants born to mothers infected during the first half of pregnancy and may result in miscarriage, stillbirth, mental retardation, sensorineural deafness, cataracts, and heart disease. The risk of congenital rubella infection in seropositive pregnant women appears to be relatively low. In one study the intrauterine infection rates were 10%, 11.8%, 2.9%, and 6.5% after maternal infection at 1–10, 11–14, 15–19, and 20–29 weeks' gestation, respectively. Six of 95 fetuses from rubella-infected mothers had serologic evidence of congenital infection. Among the six fetuses, one had CRS with sensorineural deafness, two were terminated at midtrimester, two were normal, and one was lost to follow-up. No evidence of rubella defects was found in the other 81 children during a two- to four-year follow-up period.[119]

Hantavirus pulmonary syndrome

Hantaviruses are rodent-borne bunyaviruses that lead to two clinical disease states in humans: hemorrhagic fever with renal syndrome, and hantavirus pulmonary syndrome. A North American

hantavirus was first identified in 1993 as a cause of acute pulmonary edema, respiratory failure, and shock with a mortality rate >50%.[122] Fortunately, hantavirus infection in pregnancy is rare, with few reported cases of hantavirus pulmonary syndrome. One case describes a 29-year-old woman with persistent, high fever for six days, no fetal movement for two days, frequent vomiting, headache, lumbodynia, and orbital pain. On examination, she had a normal body temperature, facial flushing, conjunctival congestion, pharyngeal congestion, bulbar and conjunctival edema, severe jaundice, petechiae and ecchymoses at sites of venipuncture, abnormal liver and renal function tests, heavy proteinuria and hematuria, and coagulation disturbance. A diagnosis of hemorrhagic fever with renal syndrome was confirmed with an antihantavirus IgM titer of 1:20. Her condition rapidly deteriorated, with frank hematuria, oliguria progressing to anuria, and shock. Hemodialysis was started and a stillborn male infant, of 3200 g, was delivered vaginally following induction of labor 12 hours later. The fetus showed no obvious abnormalities, but the parents declined an autopsy. Following delivery the patient recovered and was discharged three weeks later. The repeat titer for antihantavirus IgM was 1:80 ten days after presentation.[123]

An outbreak of hantavirus pulmonary syndrome occurred in the western United States in the 1990s. Five pregnant women were affected at gestational ages from 13 to 20 weeks. Although no placental transmission of hantavirus was evident, two fetal losses and one maternal death occurred. Fetal losses were related to severe hypoxemia and lactic acidemia. The disease was similar in pregnancy as in nonpregnant patients, although fevers were noted to be lower in the pregnant women.[124,125]

No specific treatment for hantavirus exists, so anesthetic care is supportive. The hemorrhagic nature of the disease usually precludes regional anesthesia and pulmonary involvement may complicate GA. Human-to-human transmission has been reported for hantavirus (incubation period 15–24 days)[126] so standard barrier precautions should be used.

Emerging infections

Emerging infections include West Nile virus (WNV), monkeypox, and severe acute respiratory syndrome (SARS). West Nile virus, like avian influenza, is primarily a disease of birds, but is spread by mosquitoes. National blood donor screening for West Nile virus RNA suggests asymptomatic infections are widespread with approximately 735 000 cases occurring in the United States in 2003.[127] West Nile virus causes significant neurologic disease in a small portion of infections (1 per 256 cases). A severe case of neurointensive illness in a parturient was reported by Skupski and colleagues.[128] After elective termination, fetal tissues showed no evidence of WNV transmission. However, intrauterine WNV infection can occur. In one WNV epidemic in Colorado, 4% of cord blood samples were positive for WNV-specific immunoglobulin G antibodies.[129] Currently it appears that the risk to the fetus from maternal WNV infection is low although a congenital WNV syndrome has been described.[130]

An outbreak of monkeypox occurred in the United States in 2003.[131] The infection was related to exposure to infected prairie dogs but no human-to-human transmission was known to occur, although such transmission has been reported during an outbreak in the Republic of the Congo.[132] No mother-to-fetal transmission of the disease has been reported.

Severe acute respiratory syndrome, a highly contagious infection caused by a strain of coronavirus (SARS-CoV) produced numerous deaths during an epidemic in Hong Kong and Toronto in 2003. Severe acute respiratory syndrome has been reported in pregnancy, with subsequent delivery of an uninfected, healthy baby.[133] Overall, however, adverse outcomes in mothers with SARS are usual, with 57% of patients presenting in the first trimester with spontaneous miscarriage. The remaining pregnancies are often complicated by preterm delivery and IUGR.[134] Pregnant women do worse than nonpregnant women with SARS, having more renal failure and DIC.[135] Stepwise protocols for handling outbreaks have been developed.[136]

Other viruses

A classification of viruses including other viruses causing human infection is shown in the Appendix to Chapter 18.

Tropical diseases

Dengue virus

Dengue fever is caused by a flavivirus and is likely the most important arthropod-borne viral disease in the world with an estimated 50–100 million cases annually. In most cases, it is a benign acute febrile illness with few consequences. However, in less than 1% of cases, particularly after a secondary infection by a different dengue virus serotype, the virus may cause severe disease manifested primarily as a bleeding diathesis known as dengue hemorrhagic fever (DHF).[137] About 20–30% of those with DHF develop dengue shock syndrome (DSS) that, if untreated, has a mortality of 50%. The severity of secondary infections may present problems in vaccine development, particularly if immunity is achieved against only some of the serotypes.[138] Some viral infections (including dengue, Ebola,[139] and HIV, among others) may exhibit antibody-dependent enhancement (ADE) of infection where, in the presence of virus, reactive antibody increases viral entry into target cells. The development of DSS has been attributed to ADE.[140]

Dengue is transmitted by mosquitoes (*Aedes aegypti)* that carry dengue virus types 1, 2, 3, or 4. Most cases involve type 1. Dengue hemorrhagic fever is characterized by intense, sustained abdominal pain; persistent vomiting; sudden change from fever to hypothermia; and marked restlessness or lethargy. Hemoconcentration may occur. Confirmatory diagnostic tests include capture ELISA, rapid immunochromographic tests, and polymerase chain reaction (PCR). The number of female mosquitoes, *Aedes aegypti*, in a household is a significant risk factor in outbreaks of the disease.[141] Notably, the characteristic feeding and breeding patterns of these mosquitoes in southwestern United States (Tuscon, Arizona) suggest dengue fever outbreaks could occur in the US.[142] Clinical manifestations, laboratory

Table 18.3 Dengue disease

	Clinical manifestations	Hematology	Treatment
Dengue fever (self-limited viruses)	(a) 4–5 day incubation period; sudden fever (39.5–41.4°C); intense headache, generalized muscular pain, periorbicular and joint pain, lymphadenophathy, and anorexia (5–7 days). (b) In two thirds of cases, a maculopapular blanching rash may appear on the third day, with petechiae in the axilla and on hands or feet. There is a pulse/temperature dissociation (i.e. high fever and low pulse rate). May have bone pain lasting several weeks although such pain is absent in DHF/DSS. Depression and fatigue generally persist after resolution of acute symptoms.[143]	Leukopenia, relative lymphocytosis, and mild to severe thrombocytopenia.	Symptomatic treatment. Avoid nonsteroidal anti-inflamatory drugs, which may impair coagulation.
Dengue hemorrhagic fever – dengue shock syndrome (DHF-DSS)	Most cases occur during a second DV infection; severity varies from insignificant to life-threatening bleeding with death within 12–24 hours in the absence of adequate symptomatic treatment.[143,144] Abdominal pain mimics an acute abdomen. Hypotension with narrowed pulse pressure from intravascular volume depletion. Antibody-dependent enhancement of DV growth in mononuclear phagocytes is thought to be the mechanism whereby preexisting dengue antibodies confer excess risk for DHF-DSS.[145] Interleukin-1[146] and plasminogen cross-reactive antibodies[147] may play an important role in the etiology of DHF-DSS.	Leukopenia, lymphocytosis, and thrombocytopenia.	As above; there is no way to prevent hemorrhagic sequelae.

signs, and treatment are described in Table 18.3. After resolution of the disease, mental depression and fatigue generally persist.[143]

It is unknown whether dengue virus infection during pregnancy causes teratogenicity, abortion, or IUGR. Chong and Lin reported nine cases of women infected with dengue fever in early pregnancy who received amniocentesis or chorionic villus sampling. The chromosome analysis was normal, and the level of alpha-fetoprotein in amniotic fluid and maternal sera was within the normal range. Anti-dengue activity was found in the lipid component of human milk and colostrum. This suggests that breast feeding will protect the infant from the dengue virus in the endemic area of dengue infection.[148] In contrast to this report, however, some have reported a high incidence of prematurity, fetal distress, and occasional fetal death.[149,150] Mother and fetus are at risk from hemorrhagic events when dengue infections occur near the time of delivery.[149] A live attenuated vaccine should soon be available for dengue virus. In addition, a DNA vaccine against the nonstructural 1 protein of dengue 2 virus is under development in Brazil.[151] However, as antibodies to all four serotypes of dengue can cross the placenta to the fetus and persist in the fetus for nearly a year, vaccination of the infant in endemic areas is not recommended until one year of age.[152]

Vertical transmission of dengue fever is sporadic and most often the neonate recovers uneventfully. However, neonatal death from uncontrolled intracerebral hemorrhage and multiorgan failure has been reported.[153]

A self-limited dengue fever should be treated symptomatically. It is better to avoid NSAIDs for fever because of the possibility of worsening any coagulopathy. Cyclooxygenase-2 inhibitors may be a good alternative. Neuraxial anesthetic techniques should be avoided during the active viral phase due to neurological manifestations of dengue, the frequency of which is unknown. In a review of 41 cases with neurologic symptoms,[154] it was found that dengue involved regions of the brain (61%), spinal cord (6%), and peripheral nerves (34%). Intravenous or inhalational analgesia may be alternatives to regional anesthesia during labor. Dengue hemorrhagic fever/dengue shock syndrome requires aggressive fluid resuscitation, effective utilization of blood bank technology, and preventive measures during delivery to minimize blood loss. Emergency C/S usually requires GA, with ketamine a recommended induction agent.

Yellow fever virus

Yellow fever (YF) virus was first recorded in Barbados in 1647. This virus is transmitted between individuals by infected mosquitoes including the *Aedes* species, *Haemagogus* species, and others. The fatality rate of severe YF is approximately 20%,[155] but can be as high as 57% in individual epidemics.[156] Clinical management, laboratory signs, and treatment are described in Table 18.4. Diagnostic serology involves IgM antibody capture enzyme linked immunosorbent assay (MAC-ELISA), ELISA inhibition, or neutralizing antibodies.[155]

The 2002 Yellow Fever Vaccine Recommendations of the Advisory Committee on Immunizations Practices reported that YF vaccine is considered to be one of the safest and most effective live virus vaccines ever developed. Nonetheless, the report also details vaccine-related complications including vaccine-associated neurotropic disease (encephalitis), and vaccine-associated viscerotropic disease (febrile multiple organ system failure). The incidence of these severe life-threatening

Table 18.4 Yellow fever

Clinical findings	Yellow fever is characterized by a biphasic illness: (a) First stage: after 3–6 day incubation period ⇒ fever, rigors, headache, backache, myalgia, and prostration, which improves in 2–3 days. (b) After one day of apparent cure, a flushed face, swollen lips, bright red tongue, nausea, bradycardia, vomiting, tendency to bleed (black vomit, melena, bleeding gums, ecchymoses); may result in hepatorenal failure and death. The disease can progress from prodrome to death in 7–10 days.
Laboratory findings	(a) First stage: lymphocytosis. (b) Albuminuria, oliguria, anuria, electrolyte imbalance, thrombocytopenia (signs of hepatic and renal failure).
Treatment	Symptomatic, best in a hospital setting (antiemetics, acetaminophen, avoid nonsteroidal anti-inflammatories that can impair coagulation). Serum electrolytes and acid-base balance should be estimated daily. Few cases may require hemodialysis, cardiotonic drugs, or monitoring of respiratory function.
Prevention	Highly effective vaccine is available.

disorders among those vaccinated in the United States is estimated to be 1:400 000.[155]

The safety of YF vaccination during pregnancy has not been established and it is recommended only if travel to endemic areas is unavoidable. Vertical transmission from the vaccine is very low (1 in 81) and is not associated with congenital anomalies.[155,157] Yellow fever vaccination may be associated with an increased risk of spontaneous abortion.[158] The developing nervous system is particularly sensitive to the effects of YF virus and some believe that vaccination should be avoided during pregnancy since the live virus is transmissible to the fetus.[159] However, the high risk of natural infection plus maternal death during YF epidemics may outweigh the theoretical contraindications to vaccination. The relative safety of vaccinating pregnant women is supported in a review of 480 pregnant women who received YF immunization before pregnancy was diagnosed.[160] Maternal seroconversion was very high when immunization was carried out in early pregnancy. Overall, first trimester vaccination did not cause malformations, CNS complications, or adverse perinatal outcomes.[160]

Despite numerous reports of YF during pregnancy and the puerperium, obstetric anesthesia concerns during YF have not been described. However, as neurologic disease may result and coagulopathies may occur, the risks of regional techniques may outweigh the benefits in many cases.

Leptospira species

Leptospirosis occurs worldwide but is most common in temperate or tropical climates. It presents an occupational hazard for people who work outdoors in contaminated areas or with animals, for example, farmers, sewer workers, veterinarians, fish workers, dairy farmers, or military personnel.[161] The pathogenic spirochetes are classified into a variety of serogroups and serotypes including *fortbragg*, *hardjo*, *interrogans* (*icterohaemorrhagiae*), *autumnalis*, *bataviae*, *canicola*, *pomona*, *grippotyphosa*, *javanica*, *mankarso*, *djasmani*, *cynopteri*, and others. Each serotype tends to be associated with a particular vertebrate that acts as a natural reservoir. Human infection is acquired through mucosal or skin contact with a contaminated substance, such as urine or feces. The organism is not spread from person to person. The Spirolept human vaccine induces a protective response against *Leptospira interrogans ss icterohemorrhagiae*, a serogroup that can be transmitted to the animal model and is linked to a humoral response.[162] Leptospirosis has a well-known abortive effect in animals and is thought to lead to perinatal deaths in endemic areas.

Table 18.5 Leptospirosis

Clinical findings	Vary greatly with most infections being subclinical. 5–10% result in severe infection.[164] (Following 1–2 week incubation period, after penetrating the skin or mucosa, the leptospiretes invade the bloodstream and spread throughout the body causing hepatomegaly, meningitis, pancreatitis, diarrhea, hemorrhage, hypotension, and ARDS.) Severe fatal form usually presents as hepatorenal failure although any organ may be involved. Abdominal pain and vomiting (71.4%) are major presenting symptoms in the severe form. Coagulation abnormalities may contraindicate neuraxial block.[165] Mortality rate is 1–5%.[161]
Treatment	i.v. penicillin; doxycycline is an alternative therapy.[161]

The clinical manifestations and treatment are described in Table 18.5. The diagnosis can be established by serological investigation and isolating the leptospire. The most important ingredient for the control of preventable infectious diseases is "political will".[163]

Plasmodium species (malaria)

Malaria is a tropical parasitemia transmitted by mosquitoes (*Anopheles* spp.) infected with *Plasmodium* spp. (*vivax, falciparum, malariae*, or *ovale*). It is responsible for 11% of deaths in children within developing countries despite the fact that treatment of malaria is quite inexpensive (US$0.13 for chloroquine; US$2.68 for a seven-day course of quinine in 2004).[166] The disease predominates in the rainy season or near water sources. A complete diagram of the life cycle of malaria is available at www.cdc.gov/malaria/biology/life_cycle.htm. Infectivity can be measured by the numbers of parasites in peripheral blood using the conventional Giemsa-stained blood smear, which remains the gold standard for laboratory confirmation of the disease. The sequestration of erythrocytes containing mature

Table 18.6 Manifestations and treatment of malaria

Clinical manifestations	(a) 85–90% of parasitemic episodes are asymptomatic. An estimated three to four 48-hour cycles of schizogony may occur without eliciting either fever or macrophage activation. Fever develops, followed a day later by a spike in urinary neopterin, a product of monocytes/macrophages.[168]
	(b) If symptomatic: recurrent episodes of fever and shivering are related to the cycles of intra-erythrocytic schizogony; vomiting, anemia; splenomegaly and muscle pains occur. Headache, convulsions, and mental slowness, in cerebral malaria, icterus or acute renal failure may occur. Hemoglobin <8 g/dl is associated with IUGR. The mother may develop pulmonary edema and hypoglycemia[169] in the third trimester. Hypoglycemia is possibly due to inhibition of gluconeogenesis caused by failure of hepatic lactate uptake. There is a 50% reduction in serum vitamin A, due in part to impaired hepatic function.[170]
Treatment	Traditional seven-day course of quinine therapy is associated with a 50% failure rate in pregnant women.[171] Pregnant patients may require multidrug therapy or larger dose of mefloquine, in order to achieve comparable blood levels, due to increased volume of distribution.[172] The combination of pyrimethamine/chloroquine appears to be highly effective.[173]
	Chemoprophylaxis or avoidance of exposure are the only measures likely to protect both mother and baby.

forms of *P. falciparum* in the microvasculature of vital organs may cause large discrepancies between the peripheral blood parasite count and the total body parasite burden.[167] Clinical manifestations and treatment are described in Table 18.6.

Malaria in pregnancy increases maternal and perinatal morbidity and mortality. Pregnancy is associated with increased susceptibility to *falciparum* malaria, especially in primigravidae,[174] and pregnant women are three times as likely to develop severe disease than nonpregnant women in the same area. The placenta appears to be a preferential site for parasite sequestration and replication. Indeed, the placenta may be black with malarial pigment, even when the mother is asymptomatic.[175] Malarial infection may lead to miscarriage, premature delivery, low birthweight, congenital infection, and/or perinatal death.[166] Most malarial infections may be treated with chloroquine or quinine and clindamycin. Optimal therapy depends on knowledge of the area where the disease was acquired and likely drug resistances. Alternative drugs, e.g. mefloquine and primaquine, are generally not recommended in pregnancy. An increase in stillbirths has been reported with mefloquine.[176] McGready and colleagues reported the relatively safe use of artemisinin derivatives in women with multidrug resistance, recrudescent infection, or hyperparasitemia.[177]

Severe malaria in the pregnant woman is treated with parenteral quinidine gluconate in a dose sufficient to maintain a quinidine level of 3–8 mg/l for at least 24 hours (loading dose followed by infusion). At these doses, quinidine may have significant cardiac effects including ventricular dysrhythmia, hypotension, and prolongation of the QTc interval.[178] It may also cause hypoglycemia. However, as most deaths from severe malaria occur within the first one to two days, the use of a loading dose is recommended. Finally, should parasite density exceed 10%, or if cerebral malaria, nonvolume overload pulmonary edema or renal failure occur, exchange transfusion may be used to reduce parasite derived toxins and cytokines.[179,180]

There are no reports detailing obstetric anesthesia in women with malaria. Anesthetic concerns would include the theoretical risk of CNS infection from transfer of infected erythrocytes during dural puncture, exacerbation of hepatic dysfunction by anesthesia-induced hypotension, and accentuation of maternal anemia by excessive preanesthetic hydration. As malaria may affect virtually any organ system, the precise interactions of malaria with an anesthetic technique would depend on the organ systems affected.

Mycobacterium tuberculosis

Tuberculosis (TB) is estimated to infect one-third of the world's population, with most of those affected living in developing countries. About 10% of infected patients will develop symptoms of disease, but this number is rising as a result of HIV coinfection.[181] Individuals in certain occupations have an increased risk of TB (see Table 18.7).[182]

Each year approximately 2 million deaths occur worldwide from TB, 98% of them in developing countries.[181,182] After a steady decline in TB rates from 1953 to 1985, the United States had a resurgence of TB in the late 1980s and early 1990s due to increased immigration from countries with high prevalence, HIV infection, emergence of resistant strains, poverty, homelessness, drug abuse, and a decline in TB-related health services.[182,183] Cases began to decrease again in 1993 after the institution of control measures. In 1998, 18 361 cases of TB (6.8 per 100 000 population) were reported to the CDC, a 31% decrease from 1992.[182] This downward trend in case numbers has continued although at a slower rate with 14 093 TB cases (4.8 per 100 000) reported in 2005. This represents the fewest cases recorded since national reporting began in 1953. Although the numbers of cases are decreasing, not all data are reassuring. For example, the incidence of TB in minorities is significantly higher than that in whites. Also, the number of multidrug-resistant cases increased 13% from 2004 to 2005.[184] Nevertheless, based on the decrease in the number of work-related TB cases among healthcare workers in San Francisco, it appears better control measures work and lower the risk of TB in this high-risk group.[185] Control measures

Table 18.7 Personnel with increased risk of tuberculosis[182]

Hospital employees in wards with TB patients
Nurses in hospitals, especially those caring for HIV-positive or drug-addicted patients
Pathologists and laboratory workers
Respiratory therapists and physiotherapists
Physicians in internal medicine, anesthesia, surgery, and psychiatry
Nonmedical hospital personnel in housekeeping and transport work
Funeral home employees
Prison employees

Table 18.8 Fundamental principles of the DOTS strategy for tuberculosis eradication[186]

Political will
Diagnosis by sputum microscopy
Directly observed standardized short-course treatment
Adequate supply of good quality drugs
Systematic monitoring and accountability

developed by the World Health Organization are known as the DOTS strategy[186] (directly observed therapy short-course; see Table 18.8). Included in its five-element approach is direct observation of treatment results, which now is considered by many to be a standard of care in TB therapy.[181]

Clinical manifestations of TB include an unremitting cough, fatigue, weight loss, loss of appetite, fever, hemoptysis, and night sweats. Tuberculosis may include both pulmonary and extrapulmonary disease, and it mimics many disease states. In one case series in pregnant women, CNS involvement was very common but symptoms suggestive of TB during the pregnancies were uncommon. Tuberculosis should be considered in the differential diagnosis of postpartum fever of unknown origin. Sputum microscopy is the most important conventional test for TB and is adequately specific but lacks sensitivity. Detection of *Mycobacterium tuberculosis* by culture requires six to eight weeks. More ideal diagnostic procedures, e.g. polymerase chain reaction assays with excellent specificity and sensitivity for bacilli detection, and identification directly from clinical specimens, have been developed.

Pregnancy does not change the course of tuberculosis but, unless treated, TB poses a risk to the pregnant woman and her fetus and peripartum TB is often severe. Treatment of pregnant women should be initiated whenever the probability of TB is moderate to high. Infants born to women with untreated TB may be of lower birthweights than normal and, rarely, a baby may be born with TB. Although drugs used in the *initial* treatment regimen cross the placenta, they do not appear to have harmful fetal effects. The preferred initial treatment regimen is isoniazid, rifampicin (RIF), and ethambutol daily for two months, followed by isoniazid and RIF daily, or twice weekly for seven months, and nine months of total treatment. Breast-feeding is also safe during antituberculosis therapy. Pyrazinamide is reserved for women with coinfection with HIV as its potential for fetal toxicity is uncertain, thereby contraindicating routine use.[187] Many agents used to treat TB have the potential for significant maternal side effects. For example, adverse effects of rifampicin include renal failure, anemia, leukopenia, and thrombocytopenia. The major toxicities of isoniazid are on the peripheral nervous system, liver, and kidneys. Isoniazid-induced neuropathy can be prevented by administration of pyridoxine and by a reduction of the isoniazid dose in women who are slow acetylators.[188]

Maternal clinical condition and the effects of treatment will dictate the best anesthetic technique and anesthetic drugs. Care must be taken to determine the extent of systemic involvement, since nonpulmonary TB is common in reports of TB during pregnancy. Reported cases of TB during pregnancy have included TB peritonitis,[189] spinal TB,[190] and genital TB.[191] Spinal TB might be considered a relative contraindication to neuraxial block, but some cases of spinal TB have actually been discovered after neuraxial block led to spread of the TB into the paraspinous muscles or after epidural analgesia was thought to have led to infection.[192,193,194]

Schistosomiasis

Schistosomiasis (Katayama fever) results from infection with the parasitic flatworms *Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, (and rarely *S. intercalatum*, or *S. mekongi*). It is a common infection in tropical countries where bodies of water are infested with snails of the *Biomphalaria* or *Oncomelania* genera. It is not found in the United States, but 200 million people are infected worldwide.[195] Infections with schistosomiasis occur during immersion in infected waters where the larvae actively penetrate the skin and migrate predominantly to the bowel veins. Pruritus is a characteristic symptom after larval penetration and the disease is sometimes known as Swimmer's Itch. Clinical manifestations and treatment are described in Table 18.9. The disease affects mainly children or childbearing women, who cook, wash clothes, or work near contaminated lakes or rivers. It is popularly known as "water belly" in Brazil, and can present as pseudopregnancy because of ascites.

Pregnant women from endemic regions may have chronic or acute forms of the disease. Preoperative laboratory evaluations include liver enzymes, albumin levels, hemoglobin level, coagulation tests, and renal function tests. Systematic ultrasonography of the liver and spleen is used to diagnose and manage patients with chronic *S. mansoni* infection.[199] Praziquantel appears to be safe to use during pregnancy and lactation, even in the first trimester.[200,201] Antischistosomal vaccines have been investigated but none have been found effective to date. Although congenital infections have been described in animal models, vertical transmission appears unlikely or very rare in humans.[202]

Yersinia species (plague)[203]

Plague occurs after humans are bitten by fleas infected with *Yersinia pestis* and 1000–3000 cases occur annually worldwide at present (10–20 yearly in the US). Plague is quickly progressive[204]

Table 18.9 Schistosomiasis

Clinical manifestations	Infection may be asymptomatic. Usual course: 20–60 days after contamination, febrile illness with diarrhea, coughing (from lung infestations), abdominal pain, sudoresis, and anorexia; periportal thickening, liver parenchymal lesions, melenae, compensated or decompensated hepatosplenic syndrome, associated with grade II or III fibrosis and esophageal varices, hemorrhage, nephropathy, and anemia. Rare associations include ischemic necrotizing colitis[196] and carcinoma of liver. Eosinophilia is a major finding in parasitic infections.[196] Among 972 pregnant women surveyed in Tanzania, 63.5% were infected with *Schistosoma mansoni*, 56.3% with hookworm, and 16.4 % with malaria; 66.4% of the women were anemic. Increased risk of anemia was associated with heavy infection with *Schistosoma mansoni* but not hookworm or *Plasmodium falciparum* parasitemia.[197] Colonic polyposis, portal and pulmonary hypertension, cystitis, and glomerulonephritis may occur.
Treatment	Oral praziquantel (a second dose nine days later is required to kill all eggs).[198] Retaining a small number of *S. mansoni* may be advantageous to people in endemic areas, in order to constantly prime the immune response. Alternative (for *S. mansoni* only) is oxamniquine.

and is characterized by bacteremia, high fever, delirium, and coma with a mortality rate as high as 90%, if not treated. Initial clinical signs include swollen and tender lymph nodes, fever, chills, headache, and exhaustion. The bubonic form is named for painful swelling of the lymph glands called buboes. Skin involvement and DIC cause red spots that turn black (hence the term – the Black Death). Bubonic plague has an untreated mortality of 30–75% and can progress to multiple organ involvement and septicemia (nearly 100% fatal). The pneumonic form becomes an epidemic easily, through aspiration of aerosolized particles, but its very high mortality (90–95%) limits spread. When diagnosed and treated, mortality is still about 15%.

Symptoms of plague take one to seven days to appear. Initial disease is marked by headaches, nausea, aching joints, fever (101–105°F), and vomiting. Buboes appear in the armpits, neck, and groin. In the pneumonic form, slimy blood-tinged sputum appears.

There are no clinical reports of the plague during pregnancy. However, related Yersinia species, e.g. *Y. pseudotuberculosis* (the phylogenetic ancestor of *Y. pestis*) and *Y. enterocolitica*, can cause abortion of the fetus in cows and sheep. Vaccines against the plague are being explored.

Vibrio cholerae (cholera)

Vibrio cholerae is the causative agent of cholera, a severe and devastating diarrheal disease. Until 1992, epidemic and pandemic cholera was associated only with the O1 serogroup of *V. cholerae*. Since then, the O139 ("Bengal") serogroup has caused epidemic cholera in a number of countries.[205,206,207] Epidemics of cholera are associated with contaminated water supply. Person-to-person transmission is rare.

Cholera-like illness is a low morbidity disease associated with eating unwashed fruits and vegetables, and drinking nonpasteurized milk and untreated water.[208] After a few hours to three-day incubation period, there is a severe acute diarrheal syndrome, with vomiting and dehydration equivalent to a loss of one liter of fluid per hour.

Vibrio cholerae is quite sensitive to acidic environments, which inhibit its growth, and consumption of a drink made from the citrus fruit toronja (pH 4.1) was protective against cholera during an epidemic in Peru. Consumption of toronja could be a useful cholera prevention strategy.[209]

The virulence of *V. cholerae* strains is, in general, ascribed to enterotoxin production. Transmission occurs via infected human excreta and may be seasonal. Prompt diagnosis is important for quick medical intervention. The Cholera Screen™ is a highly specific monoclonal antibody-based coagglutination test, with the availability of results in less than five minutes.[210,211] The vibrio are generally sensitive to tetracycline, doxycycline, azithromycin, amoxicillin, betalactams, and fluoroquinolones.[212,213] Oral cholera vaccines have been developed and have varying effectiveness.[214,215] The provision of clean water and sanitation is the most important preventive measure.[216]

Preoperative care involves intense rehydration, correction of electrolyte disturbances, and improvement in nutritional status. The pregnant patient should be hospitalized during the acute phase of cholera. Anesthetic considerations in the acute phase relate primarily to the management of clinical shock, i.e. adequate peripheral and central line placement and rehydration.

Trypanosoma cruzi (Chagas disease)

Transmission of *Tripanosoma cruzi* to humans occurs when an infected reduviid bug bites and then the bite or mucosa is soiled with contaminated feces containing trypomastigotes. Acute Chagas disease is usually a mild illness (lymphadenopathy and a unilateral periorbital edema known as the Romaña sign). When the acute illness resolves, the patient enters the indeterminate phase, after which lifelong parasitemia may occur. Ten to thirty percent of infected persons will develop chronic Chagas disease years later. Chronic disease is characterized by denervation of the cardiac conducting system, resulting in cardiomyopathy,[217] and/or denervation of the smooth muscle of the digestive tract, resulting in megacolon or megaesophagus. Characteristically, 40% of patients with Chagas disease will develop impairment of the cardiac conducting system, mainly left anterior hemiblock or anterior fascicular block. Clinical manifestations of gastrointestinal tract denervation include constipation, gastroesophageal reflux disease, and dysphagia.

The incidence of maternal transmission from patients in the chronic phase is 0.7%.[218] Congenital disease occurs in 2–10% of infants born to infected mothers,[219,220] and may result in spontaneous abortion, fetal hydrops, stillbirth, or birth of a premature infant. Multiple maternal reinfections from repeated reduviid bug bites increases maternal parasitemia and worsens congenital Chagas disease.[221] Diagnosis of congenital Chagas is by histologic evidence of placental villitis. There are no satisfactory drug therapies to treat or to prevent transmission of the parasite to the offspring. Patients who develop chronic Chagas disease tolerate regional anesthesia and GA without significant difficulties and may complain of less postoperative pain than healthy patients. However, a subset of patients will have a dilated cardiomyopathy and potentially lethal ventricular dysrhythmias.[222,223] The use of etomidate and vecuronium for patients with cardiomyopathy has been recommended.[224]

Chlamydia psittaci (psittacosis)

Infection with *Chlamydia psittaci* leads to psittacosis, a pulmonary and systemic disease that is contracted from inhalation of dried psittacine bird (or sheep) excreta or handling of contaminated plumage. After replication in mononuclear phagocytes of the liver and spleen, *C. psittacci* spreads by the bloodstream to lungs and other organs. The incubation period varies from 5–14 days. Infection typically causes a mild influenza-like illness with fever, chills, malaise, cough, mild pharyngitis, dyspnea, and occasional pleuritic chest pain. Epistaxis, severe headache, and photophobia are common. A macular facial rash (Horder spots) can occur in addition to erythema multiforme and erythema nodosum.[225] Psittacosis may be associated with endocarditis, myocarditis, encephalitis, seizures, and focal neurologic lesions. Disseminated intravascular coagulation can occur in advanced cases. During pregnancy, psittacosis can present with severe headache, atypical pneumonia (mainly dependent lobes) with hypoxemia, thrombocytopenia, anemia, hepatic dysfunction, DIC, atypical pneumonia, and ARDS. Massive placental infection with impaired placental perfusion may lead to perinatal mortality. Premature birth is likely. The disease may culminate in death. Chest x-rays usually show patchy reticular infiltrates radiating out from the hilum or involving basilar lung segments. Massive placental infection with impaired perfusion can ensue. Macrolide antibiotics (doxycycline and tetracycline) are the drugs of choice but due to adverse fetal effects (tooth discoloration), a trial of erythromycin is preferred in pregnancy.[226] With persistent disease, early delivery of the fetus may provide good maternal and fetal outcomes.[226]

Typhoid fever

Typhoid is predominantly a gastrointestinal gram-negative bacterial disease caused by *Salmonella typhi* and *S. paratyphi*. Ingestion of contaminated food is followed in 6–48 hours by abdominal cramps, sustained bacteremia, high fever, vomiting and diarrhea, and occasionally colonic perforation.[227] There may be multiple organ dysfunction such as renal failure, hepatitis, meningitis, diffuse cerebral edema, brain abscesses, and epidural abscesses.[228,229] A fourteen-day course of chloramphenicol or three-day course of ceftriaxone are both effective,[230] along with supportive therapy. Since *S. typhi* can cross the placenta and lead to neonatal infection, miscarriage, or fetal death, early treatment with ceftriaxone should be initiated. The possibility of CNS spread of disease (meningitis, epidural, and cerebral abscess) limits the use of epidural and spinal anesthesia during the acute phase of the disease. Abnormal liver function may mimic hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.

Nontyphoid salmonella (*S. enteritidis)* has been reported to be a cause of congenital infection leading to premature delivery and neonatal death.[231]

Toxoplasmosis

There are no specific obstetric anesthesia issues related to toxoplasmosis, except to note that congenital infections from vertical transmission can lead to significant fetal and neonatal morbidity and mortality. *Toxoplasma gondii* is a cosmopolitan protozoan parasite of importance when occurring as a primary infection during pregnancy and in the immunocompromised host (mainly HIV-positive mothers) due to the risk of transmission to the newborn. It is important that toxoplasmosis be prevented because even infants with untreated subclinical disease at birth have developed seizures, significant cognitive and motor deficits, and diminution in cognitive function over time. Further, infants treated for a year with pyrimethamine and sulfadiazine still have cognitive function that is less than their uninfected siblings.[232] Pregnant women should avoid exposure to risk factors such as raw or undercooked meat, unwashed fruits or vegetables, and cat excrement (especially in cat litter). As most cases of maternal toxoplasmosis are asymptomatic, or marked only by nonspecific lymphadenopathy, fever, or prostration, screening may be the only way to identify infection. Less common signs of disease in the mother include myalgia, hepatitis, maculopapular lesions, and pharyngitis, which may impair orotracheal intubation.

Leishmaniasis

Leishmaniasis can occur in two distinct forms, mucocutaneous leishmaniasis and visceral leishmaniasis (kala-azar). *Leishmania panamensis, L. mexicana*, *L. tropica*, and *L. braziliensis* are the etiologic agents for mucocutaneous leishmaniasis. The mucocutaneous form of leishmaniasis is usually self limiting. Destructive lesions of the nasal, pharyngeal, and laryngeal mucosa can occur in the advanced stages of the disease and may lead to mutilation of the face and difficult endotracheal intubation.

Infection with *L. chagasi, L. infantum*, or *L. donovani* results in visceral leishmaniasis (VL).[233] This is a rare disease and only anecdotal cases of VL in pregnancy have been reported. The disease is life threatening for mothers and infants, is endemic in tropical and subtropical areas, and the possibility of vertical transmission is real.[233] Kala-azar disease is characterized by insidious fever, shivering, anorexia, nausea and vomiting, hepatosplenomegaly, cutaneous lesions, anemia, and leukopenia. The

usual presentation in neonates with congenital disease is fever, pancytopenia, and splenomegaly.[234] Most antileishmanial drugs in use are reno- and cardio-toxic.[233] The efficacy and safety of amphotericin B for mother and fetus are supported by cumulative analysis of the literature.[235]

Q fever

Coxiella burnetti during pregnancy may manifest as acute pneumonia, hepatitis, or a flu-like illness. A severe chronic form exists, characterized by endocarditis, chronic hepatitis, and chronic fatigue syndrome.[236] The impact of Q fever on pregnancy is unclear. A fetal death at 24 weeks' gestation was reported in a woman with chronic infection. The obstetrician who had contact with the infected patient presented with pneumonia shortly after the fetal demise, perhaps as a result of aerosolization of organisms from the infected placenta. The mother was treated with co-trimoxazole and the obstetrician with doxycycline.[237]

Viral hemorrhagic fever (VHF)

Four viruses cause VHF: Ebola, Lassa, Marburg, and Congo-Crimean hemorrhagic fever viruses. Although the mode for nosocomial transmission differs for each of these viruses, the limited data do not permit clear distinction.[238] The mortality rate of the Ebola VHF is 79%. Frequent symptoms include fever (94%), diarrhea (80%), and severe weakness (74%). Other symptoms include dysphagia (41%) and hiccup (15%).[239] The incubation period ranges from two days to eight weeks, depending on the etiology. The risk for person-to-person transmission of VHF is highest during the latter stages of illness, which are characterized by vomiting, diarrhea, shock, and hemorrhage. Risk factors include travel into specific local areas where VHF has occurred recently; direct contact with blood, feces, and contaminated needles and syringes; or contact with other body fluids from a person or animal contaminated with VHF within eight weeks before onset of fever. The epidemic spread can also be due to familial transmission. The local population's superstitious interpretation of the disease is a factor that must be taken into account during meetings for behavioral change of the population.[240] The virus can be detected by ELISA. Care must be taken in managing infected people and body fluids, as recommended by the CDC.

Anesthetic considerations in infectious diseases

There is no direct evidence that lumbar puncture, using proper sterile technique, facilitates CNS disease by introducing viruses or bacteria from blood into the CSF. The incidence of meningitis after lumbar puncture appears to be similar to the incidence of spontaneous meningitis in bacteremic patients,[241,242] although it is controversial.[243] The incidence of extradural abscess after lumbar extradural catheterization in obstetric patients is estimated to be 1 in 505 000,[244] as opposed to the rate of spontaneous extradural abscess formation in the general hospital population, which is estimated to be 0.2–1.2 per 10 000.[245] Hence, it may be difficult to differentiate spontaneous from lumbar puncture-induced complications.[241] Extradural abscess can develop spontaneously in the postpartum period as described after GA.[246] A disproportionate number of extradural abscesses follow thoracic extradural block, however.[247] Patients taking concomitant systemic or extradural steroids are at increased risk.[248] Subdural empyema has been described after spinal anesthesia.[249]

The most likely pathogen in spinal meningitis after regional anesthesia is *Staphylococcus aureus*, but 2.5% of CNS infections have been attributed to *Klebsiella pneumoniae*. One case report described an epidural infection secondary to cervical vertebra osteomyelitis.[250] Factors in the development of meningitis include use of opioids,[65,68] integrity of the immunologic system, bacterial/viral count, and virulence in blood/CSF. Extradural abscess may have a variable presentation making diagnosis difficult. Early diagnosis should be considered in any patient who demonstrates signs of infection, back pain, post-spinal headache, radicular pain, weakness, paralysis, or bladder dysfunction.[251] The incidence of spinal epidural abscess is rising. Although increased awareness has led to decreased mortality, morbidity remains unacceptably high, with rapid deterioration of neurological status if there is delayed treatment. Outcome is related to erythrocyte sedimentation rate, muscle strength at presentation, and speed of intervention. C-reactive protein, comorbidities, age, sex, and degree of thecal sac compression have no prognostic value. The most important factors for good outcome in spinal epidural abscess include high clinical suspicion, prompt investigation, and immediate intervention.

Patients with spinal epidural abscess may be normothermic and have normal white blood cell counts. Urgent surgery was more likely to be offered to patients presenting with neurologic deficits than with pain alone. Patients treated without early surgery were significantly more likely to deteriorate and suffer poor outcomes.[251]

In rats, dural puncture is associated with the development of meningitis, provided the animals are bacteremic at the time of the puncture. Antibiotic treatment before the puncture appears to eliminate this risk.[252] Antibiotic therapy appeared protective in eight bacteremic obstetric patients (seven had placental pathology consistent with chorioamnionitis) having regional anesthesia, with none of the patients having infectious complications such as epidural abscess or meningitis.[253] However, there are reports of meningitis and epidural abscess after spinal anesthesia, despite preoperative administration of antibiotics.[254,255]

In the absence of guidelines, the anesthesiologist must consider the risk for regional anesthesia versus GA individually, as no risk is acceptable unless there is a clear benefit. For a localized infection away from the site of needle placement, the use of extradural catheters appears to be relatively safe.[253,256] For patients with evidence of systemic infection, GA is recommended in emergency situations. If intravascular volume has been optimized, antibiotic therapy started, and the patient is responding to therapy, regional anesthesia is acceptable.

Conclusion

Many infectious diseases, especially those caused by emerging organisms, have sudden and devastating effects on the mother and fetus. In such cases, the role of the obstetric anesthesiologist

Appendix to Chapter 18 Classification of viruses infecting humans

Group	Nature	Virus (disease)
Poxviridae	dsDNA, linear	Smallpox virus, molluscum contagiosum virus
Herpesviridae	dsDNA, linear	Herpes simplex virus (chickenpox, shingles, zoster), cytomegalovirus (mononucleosis), Epstein Barr virus (kissing disease), Kaposi's sarcoma-associated herpesvirus
Adenoviridae	dsDNA, linear	Human adenovirus A to F (enteric infections, diarrhea, respiratory infections)
Papillomaviridae	dsDNA, circular	Papillomavirus (warts)
Polyomaviridae	dsDNA, circular	
Parvoviridae	ssDNA, linear	B19 virus (exanthema in children)
Hepadnaviridae	dsDNA, circular	Hepatitis B virus
Retroviridae	ssDNA, (+), linear	Human immunodeficiency virus types 1 and 2
Reoviridae	dsRNA, linear	Reovirus (respiratory, enteric infections), rotavirus A and B (diarrhea, enteric infections)
Filoviridae	ssRNA, (–), linear	Ebola virus, Marburg virus
Paramyxoviridae	ssRNA, linear	Parainfluenza virus, mumps virus, measles virus, respiratory syncytial virus, hendravirus
Rhabdoviridae	ssRNA, linear	Rabies virus
Orthomyxoviridae	ssRNA, (–), linear	Influenza virus types A–C
Bunyaviridae	ssRNA, (–), linear	California encephalitis virus, Lit Crosse virus, Hantaan virus, Sin Nombre virus, Crimean-Congo hemorrhagic fever virus
Arenaviridae	ssRNA, (–), circular	Lassa virus, lymphocytic choriomeningitis virus, Guanarito virus, Junin virus, Machupo virus, Sabia virus
Coronaviridae	ssRNA, (+), linear	Human coronavirus (respiratory and gastrointestinal infections)
Picornaviridae	ssRNA, (+), linear	Human enterovirus types A–D, poliovirus, rhinovirus types A and B, hepatitis A virus, parechovirus (human echovirus)
Caliciviridae	ssRNA, (+), linear	Norwalk virus, Sapporo virus, hepatitis E virus
Astroviridae	ssRNA, (+), linear	Human astrovirus (gastroenteric and enteric infections)
Togaviridae	ssRNA, (+), linear	Ross River virus, Chikungunya virus, O'nyong-nyong virus, rubella virus
Flaviviridae	ssRNA, (+), linear	Tick-borne encephalitis virus, dengue virus; Japanese encephalitis virus, Valley virus; St. Louis encephalitis virus, West Nile virus, hepatitis C virus, hepatitis G virus, hepatitis GB virus, Pestivirus, Hepacivirus
Deltavirus	ssRNA, (–), circular	Hepatitis deltavirus (aggravates hepatitis 13 virus infection)
Prions	(no nucleic acid, self-replicating infectious prion protein)	Creutzteldt–Jakob disease, kuru, Gerstmann-Straussler-Schenker syndrome, fatal familial insomnia

Adapted from Centers for Disease Control and Prevention. Taxonomy and classification of viruses. www.ncbi.nlm.nih.gov/ICTVdb/MCM8.pdf

may be limited to life support and/or the containment of the infectious agent. A large number of infectious agents, particularly those causing tropical disease, lead to chronic infections, often with transmission to the fetus. Unfortunately, reports detailing anesthetic management of these patients are rarely published, so the obstetric anesthesiologist must understand the pathophysiology of the disease and its clinical features in order to make rational decisions relating to anesthesia. The usual contraindications to regional anesthesia or GA should be considered. Intravenous and local techniques that preserve cardiorespiratory function should be considered in high-risk patients in whom contraindications to both regional anesthesia and GA exist.

The most effective means to control infectious diseases is prevention. Spread of infectious agents is limited by good hygiene and the use of sterile precautions. Political and economic support for preventive health measures including proper sanitation is paramount, especially in developing countries. While vaccination against disease is a helpful control measure, vaccination is not a panacea, as recent outbreaks of mumps among vaccinated young adults have shown. In infectious disease, as in anesthesiology, we must be vigilant at all times.

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19 DERMATOSES

Robert S. F. McKay and John E. Schlicher

Introduction

The hormonal environment during pregnancy leads to significant changes in the integumentary system of virtually all pregnant women. In a few, skin changes may become pathologic. Likewise, women with nonpregnancy-related skin disorders may become pregnant, and the pregnancy may affect the course of the disease or, alternatively, the skin disorder may adversely affect the mother or the fetus. This chapter will focus on (1) normal changes of the skin during pregnancy, (2) pathologic skin disorders that occur primarily in pregnant women, (3) other dermatologic disorders with significant effects on the mother and/or fetus, and (4) the anesthetic considerations for women with these dermatologic disorders. Certain diseases that affect the skin in pregnancy, such as autoimmune diseases, are discussed in detail in other chapters. These diseases may be mentioned only in passing in the current chapter, even though the degree of skin involvement may be substantial.

Functions of the skin

The integumentary system comprises approximately 16% of body weight. It is a system containing multiple tissues including skin itself (epidermis, dermis, and hypodermis), glands (sudoriferous and sebaceous), hair, nails, nervous tissue, blood vessels, and even muscle (piloerector muscles). Although considered a single organ, the skin serves multiple discrete and interactive functions. As a barrier, it protects the body from physical agents, mechanical injury, dehydration, and ultraviolet radiation. The proper balance of collagen and elastic fibers gives skin flexibility while preventing overstretching. The skin's secretory glands, fat, and vascular system help regulate body temperature. Likewise, when present, hair and the air pockets produced by piloerection may help maintain body temperature. Skin plays a significant role in vitamin D production. It contains numerous receptors that interact with the nervous system to affect the entire body. Anesthesiologists frequently use skin as a monitor of temperature, oxygenation, hydration, blood pressure, and even blood sugar (shivering, color, tone, diaphoresis, etc.). Careful evaluation of the skin can lead to the detection of many systemic disease processes including connective tissue disease, infection, diabetes mellitus, and vascular disease. Although skin changes themselves only rarely have anesthetic implications for the pregnant woman, the underlying conditions associated with such changes often have significance to the anesthesiologist. This chapter will focus on such associations and will attempt to help the clinician distinguish benign conditions from those with morbid potential. Of note, some of the conditions discussed are very rare indeed and will receive only passing mention when the anesthetic implications are trivial.

Integrity of skin function during anesthetic procedures

The important roles of skin during anesthesia are often neglected, with the anesthesiologist being especially trained to avoid disruption of the homeostasis of internal organs (e.g. cardiopulmonary system). Yet the integrity of skin functions in the perioperative period is critical to good outcome and thus a plan for proper skin care must always be part of the anesthetic management. This is particularly true when the skin is compromised by either disease or invasive techniques, in other words, in practically every anesthetic procedure. See Table 19.1.

An anesthetic plan for management of normal skin includes simple measures such as the avoidance of prolonged skin ischemia through careful positioning, minimization of dermal trauma, and avoidance of excessive heat or cold application. In skin disease, however, knowledge of the response of the damaged area to necessary interventions may be critical. Further, careful management may not directly involve the skin at all, for example, the choice to avoid epidural morphine in patients with a history of oral herpetic lesions. Perhaps the most important preventative measure in skin care is skin preparation for invasive procedures, the general guidelines of which are given in Table 19.2.

Normal skin changes of pregnancy

The skin undergoes several changes during pregnancy, related primarily to hormonal influences. Such changes may be marked but are usually benign, nonproblematic, and/or temporary, although some (such as striae gravidarum or "stretch marks") may persist long after the delivery. These normal skin changes, seen in many or most of the gravid population, are listed in Table 19.3.

Nomenclature

As discussed in the first edition of this text, the labeling of dermatoses in pregnant and nonpregnant patients has undergone numerous revisions over the years. This remains the case. Many named diseases have been found to be identical histologically, representing various clinical manifestations of the same entity. Conversely, other entities looked alike clinically, but were later found to be pathophysiologically distinct and thus given different names. Occasionally, a particular disease may have two or more distinct etiologies yet retain a single name. As yet, no universally

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Table 19.1 The effects of surgery and anesthesia on skin functions

Skin function	Effects of surgery and anesthesia	Potential morbidity
Sensory perception	Decreases or eliminates responses to noxious input.	Damage to skin itself, e.g. pressure sores. Damage to underlying tissues, e.g. peripheral nerves.
Temperature regulation	Hypercapnia and vasodilation redistribute blood. Anesthesia compromises vasoregulation and alters response of sweat glands.	Hypo- or hyperthermia.
Infection barrier	Surgery and invasive anesthesia procedures may expose internal tissues to environmental contamination, bypassing skin.	Infectious morbidity.
Immune functions	May introduce antigens. May depress immune response.	Hypersensitivity reactions. Infectious morbidity.
Cosmetic appeal	Altered by scars/skin damage Blood vessel damage.	Social morbidity. Hematologic disruptions.

Table 19.2 Skin preparation and needle guidelines for invasive procedures

Skin preparation/scrub

There is no universally accepted method for skin preparation.

Cutaneous antiseptics in common use include: 10% povidone-iodine, 70% alcohol, iodophor in alcohol, and 2% aqueous chlorhexidine (Hibiclens®). As povidone-iodine multiuse bottles may become contaminated, it is recommended that only single-use containers of this antiseptic be used.[1] Of these preparations, only chlorhexidine and iodophor in alcohol have significant residual antimicrobial activity once the skin has dried. There are concerns that chlorhexidine, despite its use as a plaque controlling mouthwash, is toxic to various eukaryotic cells and that its use near mucous membranes should be limited.

Although rubbing increases the antiseptic effects,[2] blisters or bullae should not be vigorously scrubbed as tissue damage and spread of some types of lesions may occur.

Topical antiseptics do dry the skin and this may exacerbate eczematous lesions. Treatment with skin moisturizers, e.g. petroleum jelly, may be beneficial following the procedure.

Needle instrumentation

Certain pathologic lesions, e.g. psoriasis and sarcoid, may be reactivated by trauma (Koebner response). Similarly, infection of the skin may be spread by instrumentation. Thus, avoid instrumentation of blistered, raw, open, or otherwise infected skin.

Malignant melanoma lesions should not be instrumented.

Inflammatory sites may be instrumented, but like eczematous patches, they may harbor *Staphylococcus aureus* and therefore are best left undisturbed, if possible. Concerns that instrumentation of tattooed skin should be avoided are based on the risk of a pigment-containing tissue core from a tattoo being deposited into the epidural, subdural, or subarachnoid spaces, leading to later neurological complications.[3] These concerns may be unfounded because the tattoo pigments are inert dyes (red pigment may be the exception),[4] which do not result in any bodily reactions once the initial tattoo healing process has been completed. The amount of pigment that is used in the tattoo process is quite miniscule and once the tattoo has healed, the dyes or inks are fixed in the cells within the skin, and cannot be mobilized by a needle. Thus, there is no evidence that any harm will come from placing a clean needle through a healed tattoo.[5] Shatz and coworkers reported that India ink tattooing of the colon led to no significant adverse effects in patients studied for up to 117 months.[6]

Table modified from Garahan, M. B. & Licata, A. Dermatoses. In Gambling, D. R. & Douglas, M. J. (eds.), *Obstetric Anesthesia and Uncommon Disorders*, 1st edn. Philadelphia: W. B. Saunders, 1998, p. 353.

accepted system for naming dermatologic diseases has been found, and the authors are only able to use their judgment as to the most accurate and currently accepted nomenclature.

Pruritic dermatologic diseases seen in pregnancy

The most common dermatologic complaints in pregnancy are pruritus and rash. To distinguish the various pregnancy-related disorders that present with pruritus and rash, one must know the type of lesion, its distribution, timing, and associated conditions. Table 19.4 lists a partial differential diagnosis for pruritus and rash in pregnancy.

Pruritus gravidarum

Pruritus is the leading dermatological symptom during pregnancy[8] occurring in up to 20% of all pregnancies. Skin disorders peculiar to pregnancy may be called the specific dermatoses of pregnancy and are usually associated with primary skin lesions. In contrast, pruritus gravidarum is a poorly defined condition of

Table 19.3 Normal skin changes of pregnancy[7]

Hyperpigmentation of scars, nevi, and areolae are seen, along with the midline abdominal linea nigra, and facial melasma or "mask of pregnancy."

Striae gravidarum or stretch marks can be found on the abdomen, breasts, arms, and thighs.

Vascular changes include vessel proliferation, congestion, and vasomotor instability. Varicosities, telangiectasias, and spinal angiomas are common, as well as palmar erythema, gingival swelling, and generalized edema.

Hair growth modifications rarely include hirsutism. However, the growth cycle of scalp hair changes. The growth phase (anagen) is prolonged, resulting in a thick head of hair. Postpartum, a high percentage of the follicles simultaneously enter the resting (telogen) phase, which results in the shedding of strands. This persists for several months.

Table 19.4 Differential diagnosis of pruritus and rash in pregnancy

Condition	Characteristics
Pruritus gravidarum	Absence of skin lesions; usually occurs in first trimester, no change in liver enzymes e.g. glutathione S-transferase alpha.
Polymorphic eruption of pregnancy (polymorphic dermatitis of pregnancy, pruritic urticarial papules and plaques of pregnancy, late onset prurigo)	Papules and plaques start in stria on abdomen; occurs in third trimester after 34 weeks' gestation; involvement of face, palms, or soles unusual.
Intrahepatic cholestasis of pregnancy (obstetric hepatosis)	Elevated bile acid; absence of skin lesions; occurs in third trimester, glutathione S-transferase alpha elevated.
Pemphigoid gestationis (herpes gestationis)	Vesicles and bullae involve skin but usually not mucous membranes; occurs in second and third trimesters; skin biopsy with immunofluorescent microscopy shows subepidermal blistering with basement membrane deposits of C3 complement and IgG.
Pruritic folliculitis	Small red pustules with acne-like appearance; intensely pruritic; benign; treated with benzoyl peroxide and antihistamines.
Eczema	Significantly underreported in pregnancy; history of atopy/allergies/asthma.

IgG = immunoglobulin G

pregnancy classically associated with first trimester pruritus but no obvious dermatosis.[9] Women with pruritus gravidarum do not have specific lesions but only secondary skin lesions like excoriation marks.[10] Emollients and antihistamines can usually relieve the symptoms of pruritus gravidarum. It is not clear whether pruritus gravidarum is associated with another more well-defined condition known as intrahepatic cholestasis of pregnancy (IHCP), but the terms often are used interchangeably in the literature. Intraheptatic cholestasis of pregnancy is also associated with no specific skin lesion, but it usually presents in the third rather than the first trimester. It is the most common liver disorder unique to pregnancy and the diagnosis is suggested by unrelenting pruritus, abnormal liver function tests (in the absence of viral or drug-induced hepatitis), jaundice, and elevated serum bile acids.[9] A full discussion of IHCP is presented later in this chapter.

Polymorphic eruption of pregnancy (polymorphic dermatitis of pregnancy, pruritic urticarial papules, and plaques of pregnancy)

Polymorphic eruption of pregnancy (PEP) is the most common gestational dermatosis. It appears classically as erythematous edematous papules and plaques associated with intense pruritus.[11] This dermatosis is still sometimes referred to as PUPPP, the acronym for pruritic urticarial papules and plaques of pregnancy, which was first used descriptively by Lawley and colleagues in 1979.[12] The rash generally appears after 34 weeks' gestation and occurs in approximately 1 in 200 pregnancies[13] with higher incidences in twin (2.9%) and triplet (14%) pregnancies.[14] Notably, a number of differing entities with similar clinical aspects, nonspecific histology, and negative immunoflurescence have been called PUPPP (for example, Aronson *et al.* listed three types of PUPPP).[15] Given this confusion among dermatologists, the designation "polymorphic eruption of pregnancy" (PEP) has generally replaced the term PUPPP.[16] The usual plaque and papules begin on the lower abdomen, particularly within striae, and spread to the back and proximal extremities (see Figure 19.1). Involvement of face, palms, and soles is unusual,[17,18] but may be a significant source of distress to the patient.[17] Dyshidrosis may occur occasionally.[19] It has been suggested that primiparity, multiple pregnancy, and excessive weight gain are associated features. Although intensely pruritic, the rash resolves within a few weeks after pregnancy and the condition usually does not recur. Further work-up may be indicated for atypical presentations, bullous or pustular lesions, or in a patient with systemic symptoms. Of clinical importance, the rash of PEP can be difficult to distinguish from that of pemphigoid gestationis, an autoimmune bullous disorder with potential fetal consequences that may recur with subsequent pregnancy, menses, or hormonal therapy.[17] A direct immunofluorescent skin biopsy (positive in pemphigoid) may be used to distinguish the two conditions.[20]

Anesthetic implications

It is unlikely that PEP would have a significant impact on the anesthetic management of the patient, although the avoidance of agents that release histamine seems logical. Likewise, affected skin should probably be avoided during instrumentation,

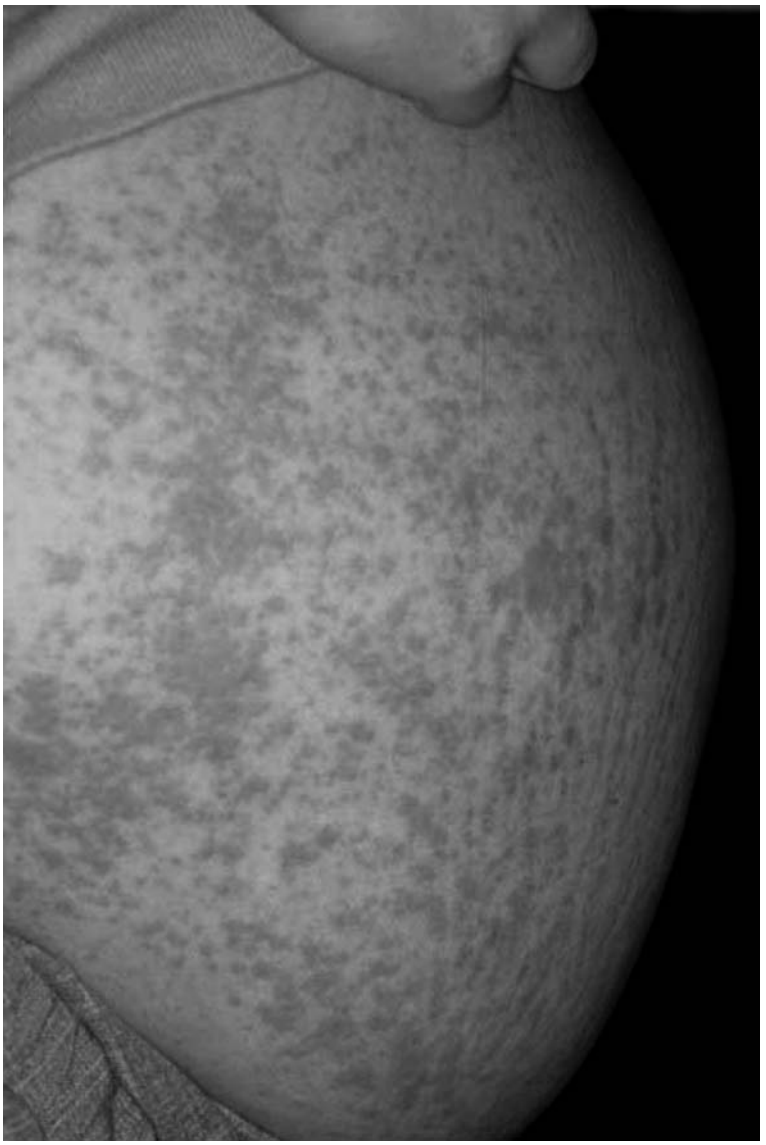

Figure 19.1 Pruritic urticarial papules and plaques of pregnancy. © Deanna Poirier, Dermatlas: www.dermatlas.org. Used with permission. (See color plate section.)

particularly since scratching of lesions by the patient might introduce bacteria at the site. It is important that the anesthesiologist does not mistakenly identify bullous diseases (the implications of which are discussed later in the chapter) as PEP.

Intrahepatic cholestasis of pregnancy (obstetric hepatosis) see also Chapter 14

Intrahepatic cholestasis of pregnancy is a pregnancy-specific liver disease associated with minimal maternal risk but a significant risk of perinatal mortality, preterm delivery, fetal distress, and meconium staining.[21] The disease reportedly occurs in approximately 1% of pregnancies at a median gestational age of 34 weeks[22] and accounts for 20% of cases of jaundice in pregnancy. Intrahepatic cholestasis of pregnancy is a genetic disorder predisposing a woman to increased cholestasis during each pregnancy or while taking oral contraceptives.[23] Among women noted to develop jaundice with oral contraceptives, 50% previously had intrahepatic cholestasis of pregnancy.[24] The diagnosis is based on pruritus (the first symptom in 97%), and elevated serum bile acids in the absence of other pathological conditions.[25] Notably, pruritus occurs in the absence of skin lesions. Although elevation of plasma bile salts is associated with itching, there is no correlation between the concentration of bile salts and severity of the itch.[26] The cause of intrahepatic cholestasis may be dysfunction of bile secretion by active hepatocellular transporters.[27] The result is the intracellular accumulation of toxic bile acids that leads to cholestatic liver cell injury. Liver biopsy shows dilated bile canaliculi, minimal inflammatory response, and nonspecific cholestasis.[28] The measurement of glutathione S-transferase alpha (GSTA, a specific marker of hepatocellular integrity) provides a test of liver dysfunction that distinguishes women with IHCP from those with benign pruritus gravidarum.[29] Serum bilirubin is also typically elevated. Although transaminases may increase, moderate to severe elevations suggest the possibility of other hepatic disease such as drug-induced or viral hepatitis. Gamma-GT is usually normal (see Table 14.5 in Chapter 14).

Although usually benign for the mother, evidence associates IHCP with poor fetal prognosis resulting from increased transfer

of bile acids from mother to fetus. This leads to an accumulation of bile acids in the cord blood serum, meconium, and amniotic fluid and may account for diminished fetal well-being and sudden intrauterine death by IHCP. Fisk and Storey[30] found low birthweight and prematurity (44%) in the more severe cases; meconium occurred in 45%. Perinatal mortality was 0.35% although this incidence did not differ from that of the general population.

When IHCP is diagnosed, ursodeoxycholic acid (UDCA) coupled with close maternal–fetal surveillance is indicated. Delivery should be effected near term following confirmation of fetal lung maturity, or earlier if fetal compromise is identified.[21] Ursodeoxycholic acid treatment reduces the bile acid content in the mother and in turn, in the fetal compartment.[31] In addition, UDCA administered to the mother lowers the amount of bile acids present in colostrum. Treatment with UDCA is especially useful in severe forms of IHCP, or when there is a history of sudden fetal death in a previous pregnancy.[32] In a series reported by Davies and colleagues,[33] twelve pregnancies were managed expectantly and perinatal morbidity and mortality resulted in eight stillbirths, two premature deliveries complicated by fetal distress with one perinatal death, and one cesarean section [C/S] for fetal distress. Subsequently, these investigators treated three women who had IHCP with UDCA. No perinatal morbidity or mortality occurred. Intrahepatic cholestasis of pregnancy starts to resolve spontaneously within 24 hours of delivery, although jaundice and abnormal liver function tests may persist for months. However, if symptoms of liver disease persist beyond this time then chronic hepatopathy must be ruled out.

Anesthetic implications

Concerns for the anesthesiologist in IHCP include the degree of hepatic disease and the possibility of planned near-term obstetric interventions (e.g. early induction of labor). Decreased small intestinal bile acid concentrations can lead to impaired absorption of fats and fat-soluble vitamins, resulting in steatorrhea and deficiencies in vitamins A, D, E, and K.[34] Although unusual, coagulopathy may occur with IHCP and a case of epidural hematoma complicating cholestasis of pregnancy has been reported.[35] Injection of vitamin K and fresh frozen plasma can prevent coagulopathy. If cholestyramine is used then prophylactic vitamin K should be used in a dose of 10 mg/day. There is an increased risk of postpartum hemorrhage so the patient should have blood cross-matched and large bore intravenous (i.v.) lines inserted.

Other causes of pruritus should be ruled out including thyroid disease, renal failure, lymphoma, anemia, and drug reactions. Physical examination should be normal in IHCP, with the exception of possible skin excoriation from scratching. Ondansetron may be effective treatment for IHCP-associated pruritus.[36] Opioids, especially neuraxial opioids, may exacerbate the pruritus, but effective pain management should be used.

Pemphigoid of pregnancy (herpes gestationis)

Milton,[37] in 1872, designated this intensely pruritic rash that may follow a viral-like prodrome as herpes gestationis, but the disorder is *autoimmune* in origin rather than viral. Pemphigoid of pregnancy (PP) is an autoimmune pregnancy-associated subepidermal blistering disease and must be differentiated from bullous pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, linear IgA dermatosis, cicatricial pemphigoid (mucous membrane pemphigoid [MMP]), porphyria cutanea tarda, and drug reactions (i.e. toxic epidermal necrolysis, Lyell syndrome, Stevens-Johnson syndrome). (See Table 19.5). Pemphigoid of pregnancy usually affects skin and, rarely, mucous membranes. The disorder occurs in approximately one in 50 000 pregnancies and usually begins in the second or third trimester and occasionally in the postpartum period. Pemphigoid of pregnancy may occur in trophoblastic disease and with oral contraceptive use.[38] The disease appears to be mediated by immunoglobulins G1, G3, and A (IgG1, IgG3, and IgA) that specifically target the 180-kD component (BP 180) of hemidesmosomes (collagen XVII). The terms *pemphigoid gestationis* or *pemphigoid of pregnancy* reflect the immunopathologic similarity to bullous pemphigoid, a disease of the elderly that also involves antibodies to the 180-kD hemidesmosomal antigen but that does not appear to show reactions to hormonal stimulation. The membrane proximal NC16A domain of this autoantigen contains key epitopes of autoantibodies and T cells and plays an essential role in the pathogenesis of both diseases as well as other blistering diseases (see Table 19.5).[39] Abnormal expression of class II major histocompatibility complex (MHC) also occurs in the placental villi of women with PP,[40] suggesting ongoing immunologic stimulation. This has led some investigators to believe that the primary immunologic event takes place within the placenta and that the skin is an immunologic bystander.[41] Pemphigoid of pregnancy is found primarily in whites as one of the specific human lymphocyte antigens associated with the disease (HLA-DR4) is seldom seen in the black population.[42] Paternal human lymphocyte antigen (HLA) type may also be associated with the development of PP.[43] Other autoantibodies may occur in association with PP. Shornick and Black found an increased frequency of Graves disease in women with a history of PP.[44]

Pemphigoid of pregnancy is characterized by intensely pruritic urticarial lesions that usually begin on the abdomen and may, at first, resemble PEP. Within days, vesicles and bullae on erythematous bases develop. The polymorphic plaques migrate outward, typically starting from the periumbilical region and spreading to the abdomen, trunk, buttocks, and extremities. Facial and oral lesions are rare. Diagnosis may be confirmed by skin biopsy with immunofluorescent microscopy showing subepidermal blistering with basement membrane deposits of C3 complement and IgG. The condition may resolve late in pregnancy, but, unlike PEP, classically flares up again at delivery then slowly resolves over weeks to months. There may also be nongestational recurrences triggered by oral contraceptives and menstrual cycles.

The disease mostly leads to maternal discomfort, but fetal and neonatal complications, including preterm delivery and low birthweight, have been reported.[54,55] Although Shornick and Black confirmed these complications, they found no increase in fetal mortality.[56]

Table 19.5 Immunopathology of specific subepidermal bullous dermatoses

Disease	Target site(s)[a,45,46] and/or pathologic findings	Clinical features
I. Autoimmune – circulating autoantibodies against basement membrane zone		
Pemphigoid of pregnancy (PP)	BP 180 (type XVII collagen) NC16A domain exclusively.	Characteristic skin lesions.
Bullous pemphigoid (BP)	N-terminal 45 amino acids of the NC16A domain of BP 180 (type XVII collagen). Intracellular regions – less frequent IgG and/or C3 along the basement membrane.	Occurs primarily in elderly; otherwise similar to pemphigoid of pregnancy.
Epidermolysis bullosa acquisita (EB)	Type VII collagen.	Bullae over areas of trauma; laryngeal stenosis may occur from dense scarring.
Dermatitis herpetiformis	IgA granular deposits in the dermal papillae of noninvolved skin.	Characterized by variable degrees of enteropathy and increased intestinal permeability; otherwise similar to bullous pemphigoid.
Linear IgA dermatosis (LAD)[47]	BP 180 (type XVII collagen); linear pattern of granular IgA along the basement membrane.	Similar to bullous pemphigoid; less frequent in females; normal intestinal findings.
Cicatricial pemphigoid (CP) also called mucous membrane pemphigoid (MMP)[48]	BP180 (type XVII collagen) NC16A domain and the C-terminus that projects into the dermal-epidermal junction; linear binding of IgG and C3 to the basement membrane zone (BMZ) anti-laminin 5 (epiligrin) – less frequent.	Mucosal involvement with little skin involvement. Frequent eye involvement with risk of blindness.
Bullous systemic lupus erythematosus (SLE)[49]	Type VII collagen.	Generalized or acrolocalized vasculitis (4–30%), livedo reticularis (22–35%), and alopecia (38–78%) frequently seen.
Lichen planus pemphigoides (LPP)	BP 180 (type XVII collagen) at a C-terminus of NC16A that is not targeted by BP or PP sera.	
II. Mutations of the basement membrane zone proteins		
Epidermolysis bullosa junctionalis	Keratin mutations.	
Epidermolysis bullosa dystrophicans (Hallopeau-Siemens)[50]	Keratin mutations. Autosomal recessive.	
III. Metabolic disorders		
Porphyria cutanea tarda[51]	Caterpillar bodies (eosinophilic, elongated, segmented bodies located within the roofs of blisters) are specific for porphyrias.	Can be triggered or worsened by pregnancy.
IV. Drug-induced		
Toxic epidermal necrolysis (Lyell syndrome/Stevens-Johnson syndrome)[52,53]		Reported in pregnancy after heparin, tocolytics, methotrexate, etc. Also reported in association with staphylococcal infections.

Table modified and classification from Megahed, M. Histology of subepidermal bullous dermatoses. *Verh. Dtsch. Ges. Pathol.* 1996; **80**: 223–8.
IgG = Immunoglobulin G; IgA = Immunoglobulin A
[a] Collagen is synthesized as procollagen and large extra domains known as propeptides are cleaved off enzymatically. Bullous pemphigoid antigen 180 (BP180, type XVII collagen) is a transmembrane glycoprotein that spans the lamina lucida of the dermal–epidermal junction. This glycoprotein's ectodomain consists of 15 interrupted collagen domains. The largest noncollagenous (NC) domain (NC16A) is located adjacent to the cell membrane and is the frequent target site in many subepidermal bullous dermatoses.

Scattered reports of cutaneous neonatal herpes gestationis[57,58,59,60] have shown the frequency of skin lesions in newborns of mothers with pemphigoid gestationis to be about 5–10% with most cases resolving after only local antiseptic therapy. The goal of therapy is to limit blister formation, secondary infection, and scarring. Symptomatic treatment consists of potent topical steroids for mild cases and systemic oral steroids for more severe cases.

Anesthetic implications

Care should be taken to avoid sites with blisters as they can easily be damaged leading to secondary infection and/or scarring.

However, as PP does not represent an infectious process, areas of skin with mild disease can be utilized for invasive procedures. Unlike the situation in MMP, the airway is not involved in PP so special precautions are not needed. Dapsone is sometimes used in the treatment of PP and has been associated with severe methemoglobinemia and fetal hypoxia[61,62] as well as hemolytic anemia, especially in patients with glucose-6-phosphate dehydrogenase deficiency.[63]

Pustular psoriasis of pregnancy (impetigo herpetiformis)

This rare pustular dermatosis is noninfectious and thus the term pustular psoriasis of pregnancy (PPP) is preferred to "impetigo herpetiformis." Pustular psoriasis of pregnancy usually occurs during the third trimester of first pregnancies[64] and is characterized by an acute eruption of erythematosquamous plaques covered with tiny superficial pustules in a herpetiform distribution (see Figure 19.2). Mucous membrane involvement is less likely. Lesions are accompanied by fever and first appear in the skin folds of the groin and under the breasts. The face, scalp, hands, and feet are often spared, although painful oral and esophageal erosions have been reported.[28] Pustular psoriasis of pregnancy can be associated with marked constitutional symptoms such as fever, chills, nausea, vomiting, diarrhea, malaise, and arthralgias. Secondary infection may complicate the rash.

The etiology of PPP is unclear but may be related to decreased levels of skin-derived antileukoproteinase (SKALP). Skin-derived antileukoproteinase is a strong and specific inhibitor of human leukocyte elastase (HLE) and proteinase 3, two neutral proteinases that have been implicated in leukocyte migration and tissue destruction. Pustular psoriasis is often a manifestation of hypocalcemia and therefore patients with PPP should be tested for maternal hypocalcemia, which when severe may lead to delirium, convulsions, and tetany. Various reported causes of hypocalcemia in patients with pustular psoriasis have included hypoparathyroidism, hypovitaminosis D, malnutrition, oral contraceptive use,[65] and severe hypoalbuminemia.[66] Lesions of PPP are expected to disappear after birth but may recur during periods of stress and during subsequent pregnancies at an earlier gestational age. Fetal concerns in PPP are related to placental insufficiency, which may be found even when the disease is controlled with corticosteroids. The placental dysfunction may increase the risks of stillbirth.

Medical management of PPP includes the administration of steroids, antibiotics (for secondary infection), and the correction of hypocalcemia. In cases where steroids have been inadequate, various immunomodulators, e.g. cyclosporine A, have been used. Lesions often return, particularly if hypocalcemia recurs. Postdelivery, persistent disease is treated more aggressively with photochemotherapy, including the synthetic retinoids etretinate and isotretinoin. The toxicities associated with both short- and long-term treatment with oral retinoids include mucocutaneous effects, adverse modulation of serum lipid levels, elevation of liver enzymes, and after long-term chronic dosing, skeletal and ligamentous calcification, and hyperostosis. Both etretinate and acitretin, like all retinoids, are known teratogens in animals and humans. Consequently, women of childbearing age are strongly advised to avoid pregnancy during treatment and up to five years following cessation of therapy with etretinate and the carboxylic acid metabolite, acitretin.[67]

Anesthetic implications

The anesthesiologist should evaluate the extent of the lesions, including the presence of mucosal lesions or secondary skin infection. The possibility of esophageal lesions should be considered when placing orogastric tubes. Lesions should be avoided during invasive procedures, e.g. neuraxial blocks. The timing and effectiveness of prior treatment and laboratory evaluations should guide the need for supplemental steroids and calcium therapy.

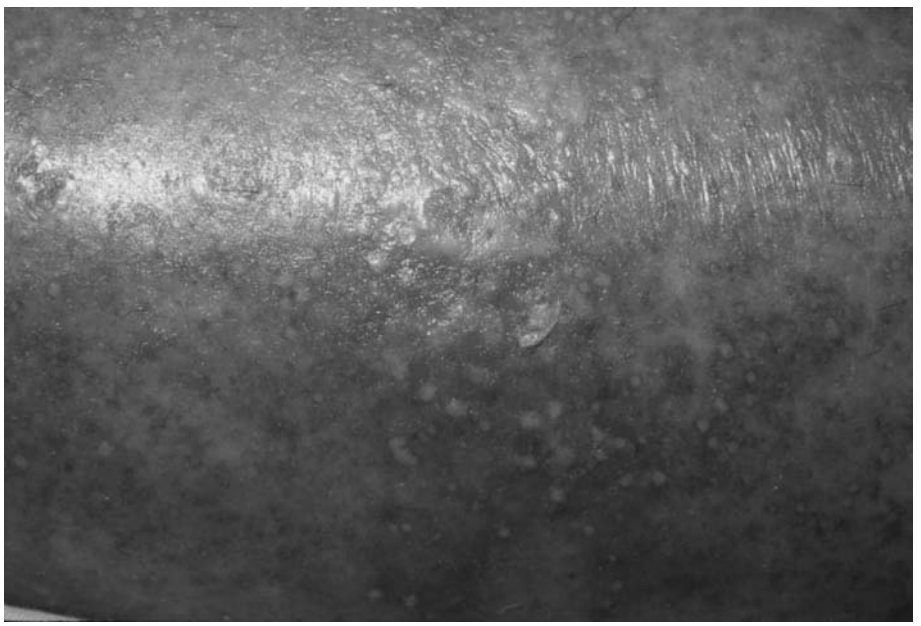

Figure 19.2 Impetigo herpetiformis. © Bernard Cohen, MD, Dermatlas: www.dermatlas.org. Used with permission. (See color plate section.)

Although severe calcium deficiency is rare, the preoperative correction of hypocalcemia with intravenous administration of 10–20 ml of 10% calcium gluconate over 1–2 min, followed by an infusion of 10 ml of 10% calcium gluconate in 500 ml of solution over six hours has been recommended by Roizen.[68] As respiratory alkalosis decreases serum levels of ionized calcium, effective analgesia should be used during labor and normocarbia should be maintained during controlled ventilation. Hypocalcemia may delay ventricular repolarization and prolong the QT interval.

Other dermatologic diseases and pregnancy

Ehlers-Danlos syndromes (Table 19.6)

The Ehlers-Danlos syndromes (EDS) are a heterogeneous group of rare inherited connective tissue disorders that are characterized by joint hypermobility, skin fragility, easy bruising, and hyperextensibility.[69,70,71,72,73,74,75,76,77,78,79,80,81,82] For a comprehensive discussion of EDS the reader is referred to Chapter 8.

Epidermolysis bullosa

Epidermolysis bullosa (EB) is a rare inherited disease marked by fragile skin and debilitating recurrent bullae or blister formation following minimal mechanical trauma. The defect is in the genes regulating keratin formation and at least 18 different mutations occur, all of which produce a fragile cell phenotype.[83] At least ten of these mutations lead to EB. Dystrophic nails and flexion contractures of the joints can lead to deformities. Carious teeth are common, and microstomia caused by scarred contractures of the lips may complicate intubation. Ocular, gastrointestinal, genitourinary, and musculoskeletal complications have been described. All types of EB have variable expression, which accounts for a broad range of clinical presentations. The most severe forms of EB include the recessive dystrophic EB (RDEB), junctional EB (JEB), EB with pyloric atresia (EB-PA), and EB simplex (EBS).[84] DNA-based prenatal diagnosis is available and genetic counseling is usually offered. Treatment is symptomatic for most types although high-dose intravenous immunoglobulin, immunosuppressants, and steroids are used in a similar disease, epidermolysis bullosa acquisita. Aggressive squamous cell carcinoma occurs frequently, particularly in patients with severe dystrophic EB.[85] Pregnancy rarely affects the course of EB.

Anesthetic considerations

Anesthesia for pediatric and young patients with EB has been described in many reports.[86,87,88,89] Airway complications are reported infrequently and general anesthesia is commonly used. Various authors have summarized the special anesthetic considerations for patients with EB.[90,91,92,93] Optimal positioning of the patient to avoid pressure points or tangential friction is necessary. Avoid scrubbing of the skin and subcutaneous infiltration, surgical tape, and adhesive electrodes. The eyes should be lubricated but not taped. Electrocardiographic monitoring using leads placed over sheets with water as the conductive media has been described.[94] Skin beneath a blood pressure cuff must be protected by adequate padding, and maximum intervals between measurements should be chosen. Nasal, oral, laryngeal, and tracheal manipulations should be kept to a minimum for protection of the upper airway. Fiberoptic intubation is preferred because of the possibility of microstomia and the simultaneous direct examination of the airway for lesions. In addition, oro- and/or nasopharyngeal tubes and catheters should be avoided. With care, serious complications did not occur in 67 procedures using standard anesthetic techniques, including general and regional anesthesia.[93]

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome)

Erythema multiforme (EM) is an acute, sometimes recurrent, inflammatory disease of the skin and mucous membranes. Erythema multiforme *minor* describes cases of typical target lesions, lacking mucosal involvement, and constitutional symptoms of fever, malaise, and arthralgias. Erythema multiforme *major* is a far more serious and potentially life-threatening disease with mucosal lesions and occasional multisystem involvement. Erythema multiforme is manifested as purpuric vesiculobullous target lesions accompanying macules, papules, and an urticarial-appearing rash. The lesions may occur on any part of the body and may arise suddenly, lasting one to four weeks. Target lesions show necrotic keratinocytes, dermal endothelial swelling, and papillary edema. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are similar diseases, but they generally involve more extensive skin involvement than EM with potentially high mortality rates.[95,96,97] Patients with SJS may develop large bullae with ulcerated erosions of the nose, mouth, and tracheobronchial tree. The conjunctiva, gastrointestinal mucosa, and genitourinary mucosa may be involved, leading to stenoses, including vaginal stenosis. Bacterial secondary infections are common. Serious, but rare, complications include hepatitis, glomerulonephritis, cardiac involvement, and pneumonia. Fluid and electrolyte imbalance and anemia may occur. Toxic

Table 19.6 Regional obstetric anesthesia in Ehlers-Danlos patients (see also Chapter 8)

Type of anesthesia	Procedure	Comorbid conditions	Maternal outcome	Fetal outcome	References
Single-shot spinal	Cesarean section	Mitral valve prolapse; breech	Good	Good	70,71,79,82
Epidural	Labor and vaginal delivery	History of vertebral artery dissection	Good	Good	80,82
Combined spinal epidural	Cesarean section		Good	Good	81
Caudal	Labor		Good	Good	82

epidermal necrolysis is defined by the presence of more extensive detachment of skin (>30%).

Both EM major and SJS can involve internal organs. Erythema multiforme minor usually follows recurrent herpes simplex infections and tends to be self-limiting. Erythema multiforme major is mainly related to herpes virus infection whereas precipitating factors of SJS and TEN include drug reactions (barbiturates, antibiotics, nonsteroidal anti-inflammatory agents, salicylates, anticonvulsants, and digitalis)[98] and herpes simplex virus (HSV), mycoplasma, human immunodeficiency virus (HIV), bacterial (especially *Staphylococcus*), fungal, and parasitic infection. Stevens-Johnson syndrome may also be a manifestation of collagen-vascular or neoplastic disease.

Erythema multiforme occurs primarily in young healthy persons. Although mortality in SJS is between 3% and 18%, SJS may well have its ominous prognostic connotation more as a result of inadequate treatment than as a result of the inherent clinical disease. High-dose systemic steroid therapy (oral dosage starting at >80 mg/day) will usually resolve most cases of SJS.

Anesthetic considerations

Erythema multiforme and SJS, like all subepidermal bullous dermatoses, must be managed with extreme caution with regards to possible airway lesions and with meticulous care to avoid friction over involved skin. Specific guidelines for anesthetic care are similar to those discussed above for epidermolysis bullosa.

Erythema nodosum

Erythema nodosum, the most frequent variant of the panniculitides, often follows infection with tuberculosis, leprosy, streptococcus or coccidioidomycosis, sarcoidosis, inflammatory bowel disease, or malignancies. An association with antiphospholipid antibody syndrome has been suggested.[99] When seen in pregnancy, it usually occurs during the first trimester and is not thought to affect the course of pregnancy or the fetus. The disease is characterized by a prodrome of arthralgia, fever, chills, malaise, and, rarely, abdominal pain, followed by the appearance of inflammatory tender red nodules on the extensor (anterior) surfaces of the lower extremities. The nodules may become multiple and plaques may appear on the trunk, arms, neck, and face. Although the nodules do not ulcerate, they do transform from red to a livid violet, then yellow as a bruise, during the three- to six-week course of the disease. The lesions heal without scarring or atrophy. Rarely, the disease may persist for years. Aseptic joint swelling may also occur, particularly in association with lower extremity edema. Erythema nodosum occurs primarily in women (female:male ratio of 6:1).[100,101] Overall, it is an uncommon clinical diagnosis. The average dermatologist will likely see few cases during his or her professional lifetime. Usually, erythema nodosum is a benign self-limiting clinical entity that requires little supportive therapy and no aggressive diagnostic work-up. The major exception is the patient with erythema nodosum who is febrile and cachectic. The diagnosis of erythema nodosum may be confirmed early in the disease process with a deep incisional biopsy, which will show neutrophils in the subcutaneous fat, interlobular septa, and small vessels. This stage is followed by a chronic lymphocytic septal infiltration and eventually, in rare cases, a noncaseating granuloma. A histopathologic hallmark of erythema nodosum is the presence of the so-called Mieschers radial granulomas, which consist of small, well-defined nodular aggregations of small histiocytes arranged radially around a central cleft of variable shape.[102] Due to its association with tuberculosis, a skin test for tuberculosis and a chest radiograph are indicated. The ionizing radiation from a chest radiograph is 5–10 mrads (~0.1 mGy), which is less than 5% of the maximal recommended exposure in pregnancy. The fetus should nonetheless be protected by abdominal shielding.

Anesthetic considerations

The presence of erythema nodosum should lead to an investigation of its etiology, with particular attention to infection, sarcoidosis, or underlying inflammatory bowel disease (Sweet syndrome).[103] Steroids are generally avoided. Needle placement should consider the possibility of local infection although reactive areas (nodules) are generally not infected. Overall, any anesthetic technique is generally acceptable.

Sweet syndrome

This acute febrile neutrophilic dermatosis is often associated with myelodysplastic syndromes, hematologic malignancies, or inflammatory bowel disease, but also has been related rarely to pregnancy, autoimmune disorders, and drug therapies. In addition to skin manifestations (painful erythematosus plaques that histologically show a dense dermal infiltrate of neutrophils),[104] there may be significant pulmonary involvement with respiratory compromise.[105] Treatment includes corticosteroids and other immunosuppressants. Spinal anesthesia for delivery has been described.[106]

Malignant melanoma

The estimated incidence of cancer complicating pregnancy is about 1 per 1 000 pregnancies, with malignant melanoma among the top five cancers affecting pregnant women.[107] Melanoma incidence rates are increasing dramatically and melanoma is now a major cause of cancer death in women of childbearing age. Due to changes in pigmentation during pregnancy, the diagnosis of malignant melanoma during pregnancy is more difficult.[108] Nonetheless, the characteristic ABCDE markings (see Table 19.7) help differentiate melanoma from the expected hyperpigmentation of nevi that occurs during pregnancy. The suspicion of melanoma is an indication for immediate excisional biopsy. Pregnancy itself is not thought to affect the prognosis of the disease.[109,110] Rather,

Table 19.7 Markings of cutaneous melanoma

A	Asymmetry
B	Border irregularity
C	Color variation or dark black color
D	Diameter greater than 0.6 cm
E	Evolving behavior (rather than static lesion)

the most important factor influencing the prognosis of melanoma is the stage of the disease at the time of diagnosis. Risk factors for melanoma include a positive family history, white race, light complexion, increased numbers of nevi, and a tendency to sunburn.[111] Melanoma is the cancer most likely to metastasize to the placenta and fetus. Alexander and colleagues[112] reported that cases of placental and fetal metastasis, from any tumor source, are extremely rare. They found that the fetus was affected in only 17% (15 of 87) of women who had placental tumor involvement. Forty percent of cases involving the fetus (6 of 15) were due to melanoma.[112]

Anesthetic considerations

Preoperative assessment should focus on a review of systems to determine organ involvement and also, on the particular therapies the patient has received. Although localized disease is of little importance to the anesthesiologist, melanoma may metastasize to multiple organs including liver, lung, bone, and brain. In such cases, the assessment of the functions of these organs is important before choosing the anesthetic method. Excision of a skin lesion can be performed safely using either general, regional, neuraxial, or local anesthesia.

Sneddon syndrome

This systemic disease is characterized by the association of livedo reticularis and cerebral ischemic arterial events (transient ischemic attacks, strokes, or cerebral hemorrhages). It has a predilection for the female gender and pregnancies are possible, although up to one-half of those with the disease become mentally impaired from strokes.[113] Sneddon syndrome has been linked to both the antiphospholipid syndrome (APS) and systemic lupus erythematosus and is associated with a significant rate of miscarriage and thrombosis. Livedo reticularis (LR) manifests as a reticular pattern of fragile skin blood vessels. This skin vasculopathy has been described frequently in patients with APS and its presence suggests valvular heart pathology and risk of stroke. Livedo are classified according to the regularity and thickness of the fishnet reticular pattern. The link between livedo reticularis and cardiac/central nervous system (CNS) thrombosis supports more aggressive anticoagulation in patients with livedo than in patients who have APS without this manifestation.[114,115]

Neurofibromatosis (von Recklinghausen disease)[116,117,118,119,120,121,122,123,124,125,126,127]

Neurofibromatosis (NF) is an autosomal dominant genetic disorder that causes tumors of the nervous system. This progressive disorder affects all races, all ethnic groups, and both sexes equally. Neurofibromatosis has two genetically distinct forms: NF1 and NF2. Neurofibromatosis type 1 is one of the most common genetic disorders in the United States (one in every 3 000 to 4 000 births). Neurofibromatosis was brought into public view by the 1980 film, *The Elephant Man*, which detailed the life of Joseph Merrick (1862–90). Physicians at the time Joseph Merrick lived and for nearly 100 years afterward believed he had elephantiasis, a disorder of the lymphatic system having multiple etiologies. In 1976, the diagnosis was postulated to be NF. Merrick's true condition, Proteus syndrome, a disorder of bone and skin overgrowth rather than nervous tissue tumors, was only identified in 1996.[117] There are, as yet, no reports of pregnancy in patients with Proteus syndrome.

The manifestations of NF1, including those of the skin, are listed in Table 19.8. For a comprehensive review of NF1 and NF2 the reader is referred to Chapter 8.

Table 19.8 Signs and symptoms of neurofibromatosis type 1 (see also Chapter 8)

CNS	Seizures, headaches, brain tumors, brain vascular defects, learning disabilities, mental retardation, macroencephaly, cancer, Chiari I malformation[125]
Ophthalmic	Visual impairment/blindness, optic glioma, Lisch nodules (benign iris hamartomas)
Laryngeal	Speech impairments and delays
Skin	Café-au-lait spots and/or neurofibromas of varying sizes may occur anywhere. Freckling where skin meets skin (armpits, groin, under breasts), intense pruritus
Cardiovascular	Hypertension, vessel fragility and rupture, coagulopathy
Musculoskeletal	Kyphoscoliosis, short stature, pseudoarthrosis (false joints), bone deformities
Endocrine	Delayed puberty, increase in number and size of tumors during pregnancy
GI	Chronic constipation, vomiting, diarrhea, pain

CNS = central nervous system; GI = gastrointestinal

Lobular capillary hemangioma (pyogenic granuloma)

These "pregnancy" tumors are found on the skin and the oral or nasal mucosa. Such growths occur in up to 5% of pregnant woman.[128] They are benign vascular pedunculated lesions that present as friable red nodules that bleed easily with mild trauma. A coexisting gingivitis is often present, but no link with infection has been established and thus the use of the term pyogenic is best abandoned. Yuan and colleagues have suggested that elevated levels of estrogens and progesterones during pregnancy play an important role in the development of the granulomas. They found that these hormones enhanced angiogenic factors in inflamed tissue and inhibited apoptosis of the granuloma cells to extend the angiogenic effect.[129] Radical surgical treatment, often with preoperative embolization, may be required in the extreme cases of giant tumors.[130] Otherwise, spontaneous involution occurs postpartum although recurrence during subsequent pregnancies is possible.

Anesthetic considerations

The risk of nasal bleeding with minor trauma is increased in pregnancy in general and particularly so in women with these hemangiomas. Uncontrollable gingival bleeding has reportedly

led to induction of labor with the eventual need for emergency cesarean section for acute fetal distress.[131] A complete airway evaluation is advised before induction of labor and nasal airways and nasal tubes should be avoided.

Selected viral and bacterial diseases with dermatologic manifestations

Currently available vaccines have altered significantly the incidence and management of a number of infectious diseases. These vaccines include *hepatitis A and B, diphtheria, tetanus, pertussis, haemophilus influenzae type b, poliovirus, measles, mumps, rubella, and varicella*. A recent report concluded that one-third of all children were under-vaccinated for more than six months during their first 24 months of life.[143] This finding would infer that sporadic epidemics of these diseases will occur. The clinical diagnosis will often be difficult for the current generation of physicians who have often not seen clinical demonstrations of the suspected viral exanthems. The clinical disease presentation may further be altered by partial immunity from (inadequate) vaccinations. See Tables 19.9 and 19.10.

Autoimmune diseases with dermatologic manifestations

Autoimmune diseases with dermatologic manifestations are summarized in Table 19.11. Rheumatologists now primarily treat these diseases. The more severe clinical manifestations require treatment regimens including systemic steroids, antimetabolites (immunosuppressants), and biologicals. As these diseases are all rare in pregnancy, there are few data upon which to make specific recommendations. The treatment often balances the risk of certain agents to the fetus versus the maternal benefit. Fetal morbidity and mortality arise from both the diseases and their treatments. These autoimmune diseases are discussed more fully in Chapter 23.

Biologic agents

Biologic agents are drugs that enhance or diminish immune system function to effect a specific action. The term *biologic* is used as a descriptive term for therapeutic agents with biologic properties, including monoclonal antibodies and soluble cytokine receptors. The first two biologic agents approved for use were the tumor necrosis factor (TNF)-α inhibiting agents etanercept and infliximab, both developed for the treatment of rheumatoid arthritis (RA). Biologic agents currently used in dermatology include etanercept, alefacept, efalizumab, adalimumab, and natalizumab. Additional biologic agents are being studied in order to achieve greater clinical success with fewer adverse side effects. The more severe clinical cases of both rheumatoid arthritis and psoriasis are increasingly being managed with parenteral biological therapy.

Bensen recently reviewed immunologic manipulation during pregnancy and suggests roles for intravenous immunoglobulin, plasma exchange, immunosuppressive drugs, and biologics including C1 esterase inhibitor protein, cell surface complement regulator proteins, or interleukin-3.[156] The biologics have efficacy in models of antibody-induced cell injury but clinical trials are still lacking. Patients on biological therapy must always be treated with great care at the first clinical sign of sepsis. They are also to be monitored for the presence of granulomatous disease, especially reactivated tuberculosis. As biologic agents are new, there may be unforeseen consequences of their use.[157] Various reports illustrate this point.[158,159,160] Three patients among 3000 participating in clinical trials of natalizumab for treatment of multiple sclerosis or Crohn disease developed progressive multifocal leukoencephalopathy, an opportunistic infection of the CNS caused by reactivation of latent JC polyomavirus infection, and for which there is no treatment. JC represents the initials of the first patient from which this species of human polyoma virus was isolated. It has no relationship to Creutzfeldt-Jacob disease or "mad cow" disease, both of which are caused by prions (abnormal proteins) rather than viruses.

C1-esterase inhibitor deficiency (hereditary angioedema)

C1-esterase inhibitor (C1-INH) deficiency is a rare disorder of the complement system characterized by episodes of cutaneous or mucosal edema of the skin, gastrointestinal tract, and upper airway.[161] Airway instrumentation or minor trauma may cause life-threatening airway edema. Gastrointestinal obstruction may occur. Griffiths and O'Sullivan[162] concluded that regional anesthesia is the safest anesthetic technique for a parturient with C1-INH deficiency and that airway instrumentation should be avoided when possible. Elective C/S should be considered if there are predicted difficulties with vaginal delivery. Prophylactic fresh frozen plasma can be used before labor or obstetric surgery to temporarily elevate serum levels of C1-INH, although this exposes mother and fetus to transfusion risks. C1-esterase inhibitor concentrate can be given for acute angioedema and before major surgery, and should be available in the operating room.

Autoimmune progesterone dermatitis

This disease is characterized by exacerbations during the luteal phase of the menstrual cycle and presents with recurrent angioedema, skin changes (e.g. erythema multiforme, eczema, and urticaria) and possible anaphylaxis.[163,164] O'Rourke *et al*. reported a case of autoimmune progesterone dermatitis during pregnancy. Delivery by C/S with hysterectomy and bilateral oophorectomy was planned since oophorectomy provides prolonged relief from the disease. Angioedema developed during delivery and was treated with fluids, ephedrine, phenylephrine, and epinephrine. The authors suggested spinal anesthesia to avoid airway manipulation.[165]

Mastocytosis

Mastocytosis comprises several diseases characterized by an abnormal increase in tissue mast cells. Cutaneous mastocytosis (CM) or urticaria pigmentosa is the most common form and presents as a mast cell hyperplasia limited to the skin. In the USA, of new patients visiting dermatology clinics, 0.1–0.8% have

Table 19.9 Viral diseases with dermatologic manifestations (see also Chapter 18)

Virus	Lesion	Symptoms and course	Maternal–fetal transmission	Newborn pathology	Medical therapy and effects	Anesthetic implications
Herpes simplex virus (HSV) Type 1: Usually oral involvement Type 2: Usually genital involvement	Erythematous papules, vesicles and pustules. Crusting by 7–10 days. Recurrences less symptomatic.	Primary: fever, malaise, lymphadenopathy, myalgia associated with viremia. Secondary: latency weeks to years. No viremia.	Close muco-cutaneous contact at birth. Primary: 50% Secondary: $< 1\%$	When infected, newborn mortality $> 50\%$. Half of survivors have neurologic or ophthalmologic morbidity.	Acyclovir and its analogs decrease symptoms and viral shedding. Excreted by kidney. Minimal maternal and fetal toxicity.	Primary: viremia associated with risk of spread to CNS. Regional block avoided. Viremia usually an indication for C/S. Epidural morphine may reactivate latent HSV. Secondary: regional block acceptable.
Human immuno-deficiency virus (HIV)	Lesions due to immuno-suppression. Common outbreaks include herpes-zoster (face, torso, extremities); molluscum contagiosum (widespread firm, translucent papules); candidiasis (oral and vulvar); staphylococcus folliculitis (face, thorax, back); Kaposi's sarcoma (any region).	Irreversible immune suppression with quiescent periods.	Occurs in 15–40%, probably via placenta. Transmission significantly decreased by antiretroviral therapy.	Affected babies appear disease-free for about eight months. Median survival = three years.	Zidovudine may cause maternal anemia, neutropenia, rash, and proximal myopathy. Oral ketoconazole has potential hepatotoxicity.	Strict transmission precautions. Multiorgan pathology common. Regional anesthesia likely acceptable (viral entry into CNS occurs early in disease; therefore regional anesthesia unlikely to "spread" the infection).
Human papillomavirus (HPV)	Genital papules and verrucous friable growths.	Swelling, pain, and itch in birth canal. Possible obstruction by lesions. Patient may be immunocompromised or have coexisting genital infections.	Transmitted vaginally at birth on exposure to lesions.	Latent infection associated with laryngeal papillomatosis in childhood. Latency period is up to five years.	Podophyllin, fluorouracil cream, and alpha-interferon are contraindicated during pregnancy. Acceptable therapies include laser vaporization and topical trichloroacetic acid.	Transmission hazard to health workers during laser vaporization. May need C/S due to mass effect of lesions.
Parvovirus B19	Bright red "slapped cheeks" erythema. Pink, lacy, reticulate rash on torso and extremities. Papular pruritic "gloves and socks" syndrome. Maculopapular eruptions, petechiae, and purpura.	Concurrent upper respiratory symptoms, fever, myalgia, fatigue, lymph node swelling.[132] Arthritis of hands, wrists, and knees. May act as trigger for autoimmune diseases e.g. systemic lupus erythematosus.[133,134,135]	Transplacental.	May cause stillbirth, miscarriage, or fetal hydrops with fetal complications in up to 20% of infected mothers.[136,137,138]	None.	Infection precautions. May be associated with aplastic crisis and chronic hemolytic anemia.

Rubella (German measles)	Generalized macular rash lasting three days.	Mild fever and malaise; arthralgia, neuritis, and thrombocytopenia are rare. 30% asymptomatic.	Transplacental early transmission leads to more significant pathology including demise.	Many congenital anomalies may result involving virtually any organ system.	No effective therapy although mother's disease generally requires no therapy. Immunization recommended before first pregnancy.	Anesthesiologists should be vaccinated to prevent spread.
Rubeola (measles)	Koplik spots on buccal mucosa are first pathognomonic sign (1-mm white dot encircled by rosy red ring). Followed by total body maculopapular rash beginning on head and spreading caudally.	Prodrome of fever and malaise followed by conjunctivitis and oral pharyngeal involvement. Cough persists for ten days along with lymphadenopathy and splenomegaly. Complications include pneumonia, laryngotracheo-bronchitis, myocarditis, encephalitis, and thrombocytopenia purpura.	Transplacental maternal infection may lead to preterm labor. No known related congenital malformations.	Transplacental transmission within a few days of birth leads to congenital measles, which may be mild but are fatal to 32%. Best avoided by immunizations.	Symptomatic. Aggressive treatment of secondary infections. Exposed pregnant women should receive immune serum globulin.	Oral pharynx, respiratory system, and neurologic systems may be involved.
Varicella	Primary: chickenpox – leads to erythematous rash followed by punctate vesicles that become purulent and crust. Significant itching. Secondary: herpes zoster (shingles).	Rash and symptoms last one week; Infectivity starts two days before rash and continues until all lesions crusted. Incidence: 1 in 5–10 000 pregnancies. In pregnant women, disease much worse: may get fulminant varicellar pneumonia. Women at particular risk for varicellar pneumonia are smokers and those with $\geq$100 skin lesions.[139]	Transplacental first and second trimester infection leads to congenital varicella syndrome in about 1% (limb hypoplasia and psychomotor retardation).	Neonatal varicella occurs if mother becomes infected and fetus is born before maternal antibody formation (within five days of infection). Neonatal varicella has 30% neonatal mortality so at risk infants should receive immune globulin.	Varicella-zoster immune globulin (VZIG) should be administered within 96 h of exposure to prevent maternal infection. Neonatal varicella is more severe if maternal rash appears five days before or two days after delivery. The newborn should be given VZIG immediately. Intravenous acyclovir is indicated for maternal pneumonia and severely affected neonate. Acyclovir and valacyclovir have not yet been adequately studied for postexposure prophylaxis to pregnant women or neonates.	Due to risk of pneumonia, airway manipulation should be avoided in mothers with varicella. Regional anesthesia is acceptable.[140]

C/S = cesarean section

Table 19.10 Bacterial diseases with dermatologic manifestations (see also Chapter 18)

Bacteria	Lesion	Symptoms and course	Maternal–fetal transmission	Newborn pathology	Medical therapy and effects	Anesthetic implications
Neisseria gonorrhoeae[a]	Small vesiculopustules and purpuric macules up to 2 cm in diameter. Lesions common around joints and on soles and palms. Usually have purulent cervical and urethral discharges in early infections.	Mother may be asymptomatic or have fever, arthralgia, and malaise. Complications included meningitis, myocarditis, and pericarditis.	Transmission during fetal passage through infected birth canal or transplacental. May have preterm labor and/or fetal loss.	Gonococcal ophthalmia can cause blindness. Urethritis in male offspring. Dissemination leads to meningitis and arthritis.	Penicillin or ceftriaxone preferred. Newborn treated with ophthalmic silver nitrate, tetracycline, or erythromycin.	Infection precautions.
Streptococcus spp. e.g. S. pyogenes	Cutaneous infection may be noted.	Fever, prodromal flu-like symptoms. May lead to necrotizing fasciitis and toxic shock like syndrome. Bacterial endocarditis may occur.	Direct contact in birth canal.	Fetal outcome related to maternal condition and exposure at birth.	Plasma pheresis to remove toxin, IV immuno-globulin, antibiotics. May need pressor support and ventilatory support.	Group B streptococcus prophylaxis is often given in labor or during C/S. Anaphylaxis may occur.[141]
Lyme disease[b] [159] (caused by the spirochete *Borrelia burgdorferi)*	Erythema chronicum migrans is an expanding erythematous patch with central clearing. Lesions common on thigh, groin, and axilla. Smaller, annular secondary lesions.	Flu-like symptoms common. May develop into chronic systemic syndrome marked by neurologic changes (meningitis, cranial nerve palsies), cardiac abnormalities (myocarditis, heart block), and arthritis.	Spirochete may spread to fetus transplacentally. Adverse outcomes in 32% of pregnancies (preterm labor, fetal demise, cardiac abnormality). Should examine placenta at birth for spirochetes.	Cardiac abnormality, syndactyly, cortical blindness, rash.	Doxycycline is usual therapy but is avoided during pregnancy (fetal effects). Penicillin, amoxicillin, ceftriaxone, erythromycin all used. Prophylactic antibodies after tick bites are controversial.	Depends on organs involved.

[a] Differential diagnosis includes meningococcemia, bacterial endocarditis, Rocky Mountain spotted fever, and vasculitis.

[b] The accurate diagnosis of Lyme disease is difficult. The disease occurs in three stages: early localized infection, early disseminated infection, late persistent infection. The clinical features of the three stages evolve, as do the laboratory findings. Laboratory confirmation requires the finding of specific antibodies to *B. burgdorferi* in serum. Numerous immunologic assays have been used. Extreme caution is necessary with regards to the interpretation of both the clinical and laboratory findings as there have been many false negatives and also false positives. Fortunately, treatment is generally successful.[142]

Table 19.11 Autoimmune diseases with dermatologic manifestations

Disorder	Lesion/etiology	Symptoms and course	Effects of pregnancy	Maternal–fetal transmission and newborn pathology	Medical therapy and effects	Anesthetic implications
Idiopathic inflammatory myopathies (polymyositis [PM], dermatomyositis [DM], and inclusion body myositis [IBM])[144,145]	Heliotope[a] rash, Gottron papules.[b] Necrotizing inflammatory myopathy of striated muscle; unknown etiology but autoimmune responses to various environmental and genetic factors have been proposed.[146,147]	Progressive proximal symmetrical muscle weakness; marked by relapses and exacerbations. 20% associated with malignancy; elevated CPK.	Pregnancy exacerbates maternal disease and exacerbation may continue postpartum.	High-risk pregnancy with 50% fetal loss but no congenital disease among survivors.[148,149] No newborn pathology.	During periods of activity, negative nitrogen balance from muscle wasting. Steroids and immune suppressants (e.g. methotrexate /azathioprine). Mortality reduced from 33% to 8% by steroid use.	Weakness of pharyngeal and intercostal muscles and diaphragm lead to airway and ventilatory problems including pneumonia; myocardial fibrosis may lead to heart block and LV dysfunction. Avoid malignant hyperthermia triggering agents. May have altered neuromuscular blocker responses.[150]
Pemphigus vulgaris	Flaccid blisters and erosions on skin and oral mucosa. IgG autoantibodies against desmosomal proteins in serum and epidermis.	1st or 2nd trimester or postpartum. Very rare in childbearing years.	Precipitated or aggravated by pregnancy.	Antibodies cross placenta. Transient lesions in newborn (neonatal pemphigus). High fetal mortality/morbidity with severe disease.	Plasmapheresis favored over immunosuppressive therapy.[151] Mortality about 5%.	Secondary infection may be present. Some patients have coexisting myasthenia gravis and thymoma. Airway considerations similar to those of epidermolysis bullosa (see above).
Polyarteritis nodosa[152]	Tender nodules, ulcerations, erythema. May occur after hepatitis B or β-hemolytic *Streptococcus* infection.	Affects medium-sized arteries of all organs except lung, especially kidney, liver, heart, and GI tract.	Uncertain.	Antibodies may cross to fetus. Few cases reported. Manifested by livedo reticularis, cutaneous nodules, and acral necrosis. Self-limiting in neonate.	Immunosuppressive therapy. Previously reported maternal mortality was high. (> 80%).[153,154]	Depends on organ involvement.
Scleroderma	Thick, taut, sclerotic skin, "salt and pepper" hyper- and hypopigmentation. Cutaneous ulcer of fingertips and joints. Limited disease: CREST[c] syndrome. Diffuse/systemic disease: internal organ involvement.	Excessive collagen production leads to diffuse fibrosis, especially of skin, lung, and kidneys. May develop pulmonary hypertension, renal failure, esophageal dysmotility, pericarditis, cardiac fibrosis with conduction defects.	Pregnancy exacerbates disease in half of cases. Renal crisis is major risk.[155] May have microchimerism wherein fetal cells enter maternal block and invoke the autoimmune response and systemic sclerosis.	No newborn effects but high rate of prematurity/SGA infants due to placental vascular abnormalities. No increase in miscarriages or infertility.	Vasodilators for Raynaud phenomenon. Steroids, immunosuppressants.	Consider renal, cardiac, and pulmonary involvement. May be restrictive lung disease. Vasoconstriction and skin changes make intravenous and monitoring access difficult. Need to maintain warm room to prevent Raynaud's. Airway compromise from esophageal involvement. Regional analgesia acceptable.

Table 19.11 (cont.)

Disorder	Lesion/etiology	Symptoms and course	Effects of pregnancy	Maternal–fetal transmission and newborn pathology	Medical therapy and effects	Anesthetic implications
Systemic lupus erythematosus (SLE)	Butterfly-like malar rash; generalized morbilliform eruption with edema. Progression to elevated plaques, dense scaling, severe edema, epidermal necrosis.	Fluctuating course with multiorgan involvement. May have nonerosive arthritis, Raynaud phenomenon, pericarditis, pleuritis, glomerulonephritis, renal failure, seizures, thrombocytopenia, leukopenia, and hemolytic anemia.	May be exacerbated by pregnancy. However, pregnancy does not affect long-term prognosis. Risk of maternal death is highest in the peripartum period, due to pulmonary hemorrhage or lupus pneumonitis. Increased risk of preeclampsia. May be hard to differentiate from lupus nephritis.	A 40% incidence of pregnancy loss up to 28 weeks is not correlated with disease severity but likely related to presence of lupus anticoagulant and anticardiolipin antibodies, which cross placenta. Also increased fetal risk from maternal disease. Neonatal lupus syndrome consists of hematologic, dermatologic, and cardiac abnormalities (e.g. complete heart block). Two-thirds of neonates are normal.	NSAIDs, aspirin, steroids, and heparin as needed. Immuno-modulators.	Consider systemic problems, particularly renal disease. Airway may be compromised by edema and lesions. Need to maintain warm room to prevent Raynaud disease. Vasoconstriction from Raynaud disease may make arterial line insertion more difficult and make monitoring of arterial blood pressure and pulse oximetry less accurate. Should document neuropathies preoperatively. At risk for thromboses in brain, placenta, and lower extremities. Regional anesthesia must take into account any coagulopathy or thromboprophylaxis therapies.

CPK = creatine phosphokinase; IgG = immunoglobulin G; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; LV = left ventricle; SGA = small for gestational age

[a] Heliotrope: periorbital and eyelid violaceous erythema and edema that may involve entire face.

[b] Gottron papules: similar to heliotrope but found on metacarpophalangeal and more distal interphalangeal joints and extensor aspects of knees and elbows.

[c] CREST syndrome: calcinosis, Raynaud phenomenon, esophageal strictures, sclerosis, telangiectasis.

some form of mastocytosis. Most cases (75%) occur in children but a second peak occurs between 30–49 years of age. Males and females are equally affected.[166] Systemic mastocytosis (SM) comprises multiple distinct entities in which mast cells infiltrate the skin and/or other organs. The diagnosis of SM is based on the presence of one major criterion and one minor criterion, or three minor criteria. Major criteria include the presence of multifocal dense infiltrates of >15 mast cells in bone marrow and/or other extracutaneous organs. Four minor criteria include the presence of elevated serum alpha-tryptase levels >20 ng/ml, the expression of certain mast cell surface markers, the presence of a c-kit mutation on mast cells, and the presence of >25% abnormal spindle-shaped mast cells. Cutaneous symptoms of CM include pruritus, flushing, urticaria, and dermatographism. It is important to distinguish these symptoms from those of local anesthetic (or other drug) allergy so these agents are not proscribed erroneously.[166] Symptoms in SM include syncope, gastric distress, nausea and vomiting, diarrhea, bone pain, and neuropsychiatric symptoms. There is no cure for mastocytosis but the majority of pediatric CM regress at puberty. Women with mastocytosis are fertile and pregnancy and delivery have been successful by blocking mast cell-mediated symptoms.[167] Pregnancies in women with mastocytosis may proceed normally but symptoms worsen in approximately one-third, likely because of decreased medication use (antihistamines, mast cell-stabilizing agents, e.g. sodium cromolyn, and corticosteroids are the usual therapies). Labor and delivery may progress normally with epidural analgesia reportedly used.[168,169] However, marked histamine excretion has been reported in a pregnant woman with a particularly rare form of mastocytosis (*telangiectasia macularis eruptiva perstans*). She had an anaphylactoid reaction, rash, uterine contractions, and vaginal bleeding and was successfully treated with tocolytics and antihistamines.[170] Cardiovascular collapse also has been reported.[171] Notably, in some cases including the case of cardiovascular collapse, the authors specifically reported that the patients lacked the supporting signs of histamine release such as cutaneous flushing and bronchospasm.[171,172] Interferon alpha, steroids, and purine analogs also have been used to reduce mast cell burden, with varying results. Future directions include tyrosine kinase inhibitors and bone marrow transplant.[167] Avoidance of histamine-releasing drugs is important, and a general anesthetic using remifentanil and sevoflurane has been described.[172]

Summary

Normal pregnancy is associated with many changes in the skin that have few consequences related to anesthesia. Nonetheless, the anesthesiologist should not look only skin deep when a parturient presents with skin lesions, since many such lesions suggest systemic diseases involving many organs. The presence of skin lesions should trigger a more complete physical examination, with particular emphasis on the airway, pulmonary, renal, and cardiac function. Regional anesthesia is contraindicated in only a few circumstances, but circumspection is required in many.

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20 PSYCHIATRIC DISORDERS IN PREGNANCY

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Introduction

The peak incidence of affective disorders in women occurs at 23 to 44 years of age, which coincides with the prime child bearing years. Pregnancy and childbirth represent major life stresses, as well as a time of fundamental psychological and social change. The experience of childbirth constitutes a major mental health hazard for women, with an estimated fivefold increase in the appearance of mental illness in the year following childbirth.[1] Women who are pregnant, or have recently given birth, may experience relapses of earlier mental disease or develop a new disorder. Women with psychiatric disorders become pregnant and their psychiatric condition can present management problems at different stages of pregnancy. Less commonly, previously well women may develop a major psychiatric disturbance during or after pregnancy, which may or may not herald a chronic condition. Many of these individuals take medications that have the potential to interact with anesthetic agents and other drugs. These women require considerable tact and skill on the part of their attendants.

The first three years of a consultation-liaison psychiatry service to an obstetric inpatient unit in an Australian hospital had a referral rate of 1.2% of obstetric admissions, totalling 90 consultations over three years.[2] The commonest DSM-III-R psychiatric diagnoses were personality disorders (19%), mood disorders (17%), schizophrenic disorders (15%), and adjustment disorders. Reasons for referral included coping problems, depression, anxiety or fear, and a history of major psychiatric illness.

Obstetric anesthesiologists may have their management skills tested with women who have personality disorders. These patients may be rude or complain excessively. The category of dramatic personality disorders includes histrionic, borderline, narcissistic, and antisocial. Affected women may also display poor impulse control, requiring a degree of firm professionalism. However, these women are not commonly on medication for their dysfunctional personality and interactions with anesthetic agents per se are less likely.

Women with a history of major psychiatric illness need counseling before becoming pregnant as they are at greater risk for postpartum psychoses, increasing the risk of harm to mother and child. It is important that the question of medication be discussed. This is a contentious area that many clinicians find difficult to approach. The various risks are to the fetus, the pregnant woman (due to altered physiology), the future behavioural teratogenesis in the newborn (effects on brain morphogenesis may not appear for years), and to the mother and fetus from inadequately managed disease.[3]

The aim of this chapter is to consider the anesthetic implications of conditions that arise de novo, as well as existing illnesses that may or may not be affected by the pregnant state.

Schizophrenia

The characteristic features of schizophrenia are delusions, hallucinations (auditory), disorganized speech (frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms (flat affect, alogia, or avolition). Two or more of these features are required to make a diagnosis of schizophrenia and each must be present for a significant time during a one-month period (or less if successfully treated).[4]

Schizophrenia affects 1% of the general population,[5] and although it is often more florid in the reproductive years there is a paucity of data concerning its incidence in pregnancy. The condition was formerly further subdivided into the principal subtypes of paranoid, disorganized, and catatonic, although the clinical relevance of that classification is now minimal.

A significant disturbance of one or more "major areas of functioning" occurs, such that self-care and interpersonal relationships are impaired. The disturbance has particular implications for the newborn child, whose safety is of concern if the schizophrenia is not properly managed.

Maintenance therapy consists of major tranquillizers, in either oral or injectable form. Haloperidol and the phenothiazines have been the most studied drugs of this class during pregnancy. The oral formulations include haloperidol, chlorpromazine, and thioridazine, whereas depot-injectable preparations include fluphenazine and flupenthixol.

All major tranquillizers have the potential to produce extrapyramidal side effects, hence the common practice of coadministration of atropine-like antiparkinsonian agents such as benztropine and benzhexol. If these agents are discontinued during the first trimester, the balance of risks and benefits needs to be considered.[1]

Case reports of limb reduction in babies born to women taking haloperidol have been published,[6] but the few large prospective studies conducted have not found any teratogenic action related to major tranquillizers. Chlorpromazine may be an exception, although the evidence implicating phenothiazines is based on their use in treating hyperemesis gravidarum[7] and not psychoses.

Although there is little hard evidence to associate psychotropic drugs with teratogenesis, there is an almost universal reluctance to continue necessary medication during pregnancy. This reluctance is despite the fact that clinical deterioration may occur as a result. As pointed out by Kuller and coworkers,[8] continuation of

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Table 20.1 Guidelines for antipsychotics in pregnancy

1. Avoidance during weeks four to ten postconception
2. Discontinue two weeks predelivery
3. Use potent agents
4. Discontinue if neuroleptic malignant syndrome develops
5. Resume immediately postpartum
6. Avoid antiparkinsonian drugs

medication throughout pregnancy is probably the wisest choice in someone with a history of instability without medication, even though exposure to the lowest dose is the preferred approach in the first trimester. Furthermore, patients with severe schizophrenia who are difficult to manage should be actively discouraged from conceiving until their illness is better controlled.

When it is feasible to withdraw therapy, Miller[9] has provided specific guidelines, which are outlined in Table 20.1. Antipsychotics should be avoided, if possible, during the period of highest risk (four to ten weeks post conception) and discontinued, if possible, two weeks before delivery to minimize withdrawal effects in the neonate. Resumption of antipsychotic medication should begin immediately postpartum. Potent agents should be given to minimize sedation, orthostasis, gastrointestinal slowing, and tachycardia. Therapy is discontinued if the neuroleptic malignant syndrome develops (see later). Routine antiparkinsonian agents are avoided.

Anesthetic implications

The archetypal phenothiazine is chlorpromazine, which was given the trade name Largactil because of its "large actions." The ability to exert an effect at many different receptors is a feature of most of the major tranquillizers. They are lipophilic amines whose action is on neuronal membranes. Binding sites include presynaptic and postsynaptic receptors, as well as reuptake sites for a host of neurotransmitters, including norepinephrine, dopamine, histamine, and acetylcholine.

It is the action of antipsychotics on the α-1 adrenergic receptor that has the greatest significance for anesthesiologists, because the reduction in peripheral vascular resistance can lead to orthostatic hypotension. In the anesthetized patient, hypotension, heat loss, and inadequate compensation for blood loss are complicating factors. The quinidine-like effects of these drugs can produce changes on the electrocardiogram, including increases in PR, QRS, and QT intervals. Preexisting heart block may be exacerbated.[10]

Schizophrenic women are at increased risk of peripartum psychoses, with considerable potential for self-harm, as well as harm to the neonates, if the mothers are delusional. Women with poorly controlled disease may be uncooperative and hostile when attempts are made to provide analgesia for labor pain. Paranoid patients, in particular, may suspect that the anesthesiologist means to harm them. It is useful to obtain a brief psychiatric history and ascertain whether medication has been taken as prescribed. Noncompliance, perhaps as part of perinatal deterioration, may presage a difficult interaction. Informed consent, which is traditionally a difficult area for obstetric anesthesiologists, becomes even more complicated in this clinical setting.

Consideration may be required for abandonment of regional techniques if operative delivery is necessary, on the grounds that a violent awake patient presents a threat to the safe conduct of cesarean section (C/S) anesthesia. The principal tenet for interaction with these patients is that the attending clinician should be "the ambassador of reality," and the anesthesiologist needs to be particularly sensitive to the dynamics of the situation. Emotional support and a quiet environment are important, and the need for urgent psychiatric consultation is self-evident.

Neuroleptic malignant syndrome

This rare but sometimes fatal condition is similar to malignant hyperthermia (MH), and may involve common pathways. It occurs typically early in treatment and is characterized by fever, muscular rigidity, autonomic dysfunction, leukocytosis, and impaired level of consciousness. Therapy includes resuscitation with intravenous (i.v.) fluids, aggressive cooling, and administration of dantrolene following guidelines for management of MH. An initial dose of 2.5 mg/kg can be repeated every 15 minutes until improvement or a total of 10 mg/kg has been administered. Bromocriptine has also been described in its management.[9]

Electroconvulsive therapy

Although this highly effective therapy is used most commonly in the management of major depressive illness,[11] it is sometimes indicated in the acutely psychotic schizophrenic pregnant patient when urgent control is required. Varan and coworkers[12] reported its use in the emergency management of a pregnant woman at 18 to 20 weeks' gestation who had homicidal impulses and tried to strangle a nurse. The patient responded well to modified electroconvulsive therapy (ECT) and low-dose chlorpromazine. She received a total of 12 courses of ECT with a conventional general anesthetic of 0.6 mg atropine, 80 mg methohexital, 40 mg succinylcholine, and assisted ventilation with 100% oxygen. Fetal heart rate (FHR) monitoring revealed a short-duration bradycardia coinciding with the tonic phase of the seizure. External uterine monitoring indicated no abnormal activity.

DeBattista and coworkers[13] have reported a short but marked FHR deceleration to 60 beats per minute (bpm) for three to five seconds some ten seconds after ECT was administered to a depressed 41-year-old primigravid woman. These authors speculate that activation of the sympathetic nervous system by the seizure may have played a role by reducing uterine blood flow. Unlike grand mal seizures, when hypoxia is common, anesthetized patients receiving ECT are well oxygenated. The clinical significance of decelerations is uncertain but probably of no great moment, in view of their very short duration.

Manic depressive illness

This general term embraces a number of disturbances of affect (mood), including unipolar depression, unipolar mania, bipolar

Table 20.2 Features of depression

1. Depressed mood most of the day, nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day
3. Significant weight loss
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional)
8. Diminished ability to think or concentrate

disorder, and hypomania. An estimated 10% of pregnant women develop a serious depression,[14] for which therapy may be instituted. Depression includes some or all of the symptoms listed in Table 20.2.

Maternal depression has been associated with a number of factors that predict poor neonatal outcome. Depressed women often have poor appetite and so may have low weight gain in pregnancy and are more likely to use tobacco, alcohol, or illicit drugs. All of these factors increase the risk of preterm birth, small head circumference, and low Apgar scores.

A systematic review[15] aimed at estimating the prevalence of depression in pregnancy by trimester, as detected by validated screening instruments and structured interviews, has determined that rates of depression are substantial, particularly in the second and third trimesters. Depression in the first trimester seems to occur as commonly in pregnant women as in the nonpregnant population (7.4% in this study). The figure rises to 12% for the second and third trimesters, perhaps indicating that late-stage pregnancy may be a risk factor for depression.

The authors[15] point out that even though many women are affected, it is not often appreciated that depression leads to a significant impairment in function. Depression is a leading cause of disability adjusted life years (years of life not lived due to premature death, and years of productive life lost due to disability). An estimated 10–15% of all women experience depression during pregnancy and the postpartum period.[15] One third of women who develop depression in pregnancy have their first episode of the disorder at this time. Physicians often fail to detect depression in pregnancy because even healthy women report symptoms during pregnancy that are associated with depression. These symptoms include disturbed sleep, change in appetite, and low energy. In addition, pregnancy-related medical conditions such as anemia, gestational diabetes, and thyroid dysfunction may mimic symptoms of depression. As a result there may be a delay in accurate diagnosis.

Depression is a major health problem for the world, and for pregnant women in particular.[16] Depression not only increases the risk of physical and social disability but is also associated with bad outcomes in pregnancy. These outcomes include poor health behavior, risk-taking behavior, preeclampsia, and an increased risk of progression to postpartum depression. There are significant associations between depression and increased nausea and vomiting, prolonged sick leave during pregnancy, and increased numbers of visits to the obstetrician.[17] There is also a significant increase in planned C/S and epidural analgesia in labor.

Untreated depression in pregnancy carries substantial perinatal risks.[18] These include direct risks to the fetus and infant, as well as risks secondary to the unhealthy maternal behaviors seen in depressed women. Untreated maternal depression can result in a catastrophic outcome. Too many studies focus on the potential but unproven risks of psychotropic medication (see later).[18] Women suffering from gestational depression, with its attendant biological dysregulation, may refuse treatment because of unfounded fears about teratogenesis. This is regrettable and has important implications for the mental health of the woman and the care of her child. One study showed that 75% of women who stopped taking antidepressants soon after conception had relapses, often in the first trimester, with symptoms severe enough to require retreatment.[19] However, although continuing antidepressants throughout pregnancy reduces relapses, it does not eliminate them. Pregnant women are twice as likely to have a relapse if they do not take their medication.[20]

Lithium

Mood modulation in women with a bipolar disorder is achieved commonly with lithium, but great concern has been expressed about the use of this drug in pregnancy. Avoidance of lithium in the first trimester was originally recommended, but one study of 148 women on lithium suggests that the incidence of major malformations is similar to that in a control group.[21] Ebstein anomaly (right ventricular hypoplasia, patent ductus arteriosus, tricuspid incompetence) has been associated with maternal lithium exposure. However, one review of four case-control studies involving more than two hundred infants with Ebstein anomaly[22] found none had been born to women taking lithium, so the risk is very low.

It is recommended that women with a single past episode of mania, whose condition is currently stable, consider discontinuing lithium therapy before conception.[22] Those with less stable disorders are advised to attempt temporary cessation of the drug during the embryonic period (4–12 weeks' gestation). Since severely affected women with bipolar disorders may be at risk if therapy ceases, they should continue to take lithium. Antenatal counseling and prenatal diagnosis should be offered.[22]

Tricyclic antidepressants

In the past, there were concerns that the use of tricyclic antidepressants (TCAs) led to phocomelia,[6] but this concern has not been borne out. The Finnish Registry of Congenital Malformations[23] reported no increase in congenital malformations in fetuses exposed to imipramine in the first trimester. Neonatal antidepressant withdrawal symptoms have been observed,[24] along with anticholinergic side effects (constipation, urinary retention).

The mechanism of action of TCAs was thought to be related to their ability to inhibit reuptake of neurotransmitters, especially

norepinephrine, into the presynaptic terminal, thus increasing the amount available for synaptic transmission. The efficacy of reuptake inhibitors for other transmitters (e.g. serotonin) in treating depression, combined with a better understanding of the complexities of neurophysiology, means that simple models represent only part of the explanation. Alterations in receptor sensitivity are likely to play a role, explaining the delay of two to three weeks in clinical response.

Anticholinergic side effects occur in up to 15% of patients and they are prominent in those who take overdoses of TCA. Anesthesiologists may be asked to help manage such patients when pregnancy is a complicating factor. I am aware of one unpublished case of a fatal overdose in a pregnant woman whose baby was delivered alive, only to die later. Features of anticholinergic poisoning include dilated pupils, agitation, and delirium. Convulsions and hyperpyrexia may occur. The features of TCA overdose are principally those of rhythm and conduction disturbance: all forms have been described. Prolonged QT and QRS segments point to cardiac involvement. Treatment of significant dysrhythmias has included hyperventilation,[25] which helps correct the acidosis. Sodium bicarbonate has been used,[26] although enthusiasm for its empirical use has waned.[27]

The principal side effects of the TCAs result from their nonspecific interactions with a range of receptors, including cholinergic, histaminergic, serotonergic, and dopaminergic receptors. The secondary amine TCAs (e.g. nortriptyline, desipramine) are relatively selective norepinephrine reuptake inhibitors with a more benign side effect profile than the tertiary amines. The α-adrenergic receptor blockade seen with TCAs can potentiate antihypertensive medication. This is particularly true for drugs that act in a similar manner, such as prazosin.

Because all TCAs lower the seizure threshold, care must be taken when they are given to preeeclamptic patients. Furthermore, extra vigilance is demanded when large volumes of local anesthetic are required, such as when establishing epidural anesthesia for C/S, because otherwise safe doses may lead to seizure activity.

Selective serotonin reuptake inhibitors (SSRIs)

Serotonin reuptake inhibitors are the mostly commonly prescribed antidepressants used in women of childbearing age. The SSRIs have not been associated with an increased risk for congenital malformations in children exposed to them during the first trimester. There is also no evidence that children exposed to this class of drug in utero experience long-term problems such as developmental delay.[20] Serotonin (5-hydroxytryptamine, 5-HT) is a regulatory neurotransmitter, with predominantly inhibitory effects. Serotonin inactivation occurs chiefly by reuptake, which is selectively blocked by SSRIs. As a result, serotonin levels rise in the postsynaptic cleft, leading to desensitization of presynaptic autoreceptors, increased serotonin release, and increased neurotransmission.[28]

Most of the data on teratogenesis concern fluoxetine, but there is no evidence to date that women taking the drug are at greater risk for fetal malformations or stillbirth. Although higher rates of miscarriage have been reported,[29] one study found that fluoxetine taken during pregnancy did not increase the risk of spontaneous loss or major anomalies of the fetus.[30] That same study, however, indicated that the number of perinatal complications was greater in women who took the drug during the third trimester compared with those who took it only in the first and second trimester. An editorial accompanying this publication concluded that the evidence does not prove that fluoxetine and TCAs are unsafe for pregnant women.[31] Their use involves a calculated risk, however, because of their uncertain side effects.

Initial work with sertraline suggests that it is useful in the treatment of postpartum depression and a recent *Cochrane Database* review revealed that sertraline reduced the recurrence of postnatal depression and the time to recurrence when compared with placebo.[32] A single case report suggests that levels in breast milk vary substantially over a 24-hour period, with no detectable levels in the infant.[33] Selective serotonin reuptake inhibitors and their metabolites variably inhibit cytochrome P450 2D6, which is the enzyme responsible for the metabolism of other drugs, such as antidysrhythmics, β-blockers, antihypertensives, and codeine. Women with a severe psychiatric illness may be taking multiple psychoactive drugs, with the potential for further interactions. These drugs include thioridazine, clozapine (an antipsychotic of the dibenzazepine group), and TCAs. To date, there is little evidence of clinically important interactions.[34] Importantly, SSRIs are safe in overdose,[35] but can interact with monoamine oxidase inhibitors to produce the sometimes lethal serotonin syndrome.[36]

Neonatal and pregnancy outcome data following maternal drug use during pregnancy were obtained from the Swedish Medical Birth Registry.[37] These data were compared to data from all infants in the registry after adjustment for birth year, maternal age, parity, and maternal smoking in early pregnancy. It identified 997 infants whose mothers had received antidepressant therapy after the first antenatal visit. The majority of mothers had taken SSRIs (558) while 395 had used TCAs. Women who had taken antidepressants were statistically more likely to have preterm birth (odds ratio (OR) = 1.96), low birth weight (OR = 1.98), and small for gestational age babies (OR = 0.83). These effects were similar between SSRIs and TCAs. There was an increase in neonatal respiratory distress (OR = 2.21), neonatal hypoglycemia (OR = 1.62), low Apgar scores (OR = 2.33), and neonatal convulsions (OR = 4.7). All of these effects were greater in neonates whose mothers had taken TCAs compared to SSRIs but these could have been random effects. Of the SSRIs, paroxetine produced the biggest difference, but it was not statistically significant and may have reflected a relatively small number of women using paroxetine.[37] The effects seen in newborns might be related to SSRI withdrawal.[37] Table 20.3 lists the symptoms that have been attributed to neonatal withdrawal following maternal ingestion of SSRIs. It is probable that neonatal withdrawal effects would be minimized by using the lowest effective maternal dose in the third trimester, while breast milk transfer can be treated by stopping or reducing the dose of SSRI, or by using formula milk.

Table 20.3 Frequent neonatal symptoms reported in association with maternal SSRI ingestion

Symptoms	Withdrawal syndrome	Breast-milk transfer
Agitation/jitteriness	15	4
Poor feeding	7	4
Hypotonia	7	1
Sleepiness/lethargy	0	3
Gastrointestinal symptoms	3[a]	3
Total reports	26	13

[a] In one case the symptoms may have been from breast-milk transfer.
Data derived from 26 reports of neonates with symptoms attributed to **withdrawal effects** due to maternal third trimester ingestion of SSRIs (paroxetine 10, sertraline 7, fluoxetine 7, citalopram 2). Table 20.3 presents the most frequently reported reactions. Other reactions included convulsions, tremor, fever, and respiratory disorders (respiratory depression, apnea, tachypnea). Two babies had marked extensor posturing with back-arching. The usual day of onset, if reported, was the day of birth, but ranged from zero to four days of age. The symptoms resolved in two to three days in most cases. In addition, 13 reports have been received of neonatal adverse effects probably resulting from **breast-milk transfer** of an SSRI (sertraline 9, paroxetine 2, fluoxetine 2). There was some overlap of the symptoms resulting from drug transfer into breast milk and from drug withdrawal (see table). However, sleepiness was reported only with breast milk transfer, and in two cases the baby slept for prolonged periods.
From *Australian Adverse Drug Reactions Bulletin* 2003; **22**: issue 4

Another study examined neonatal behavior comparing 17 SSRI-exposed neonates to 17 nonexposed neonates.[38] It was found that SSRI-exposed infants were healthy, but showed greater disruption of neurobehavior: specifically tremulousness and all measures of state and sleep organization. The implications for later development were unclear and the effects may well be short lived; however, further study is required.[38] The US Food and Drug Administration (FDA) has not approved any psychotropic drug for use in pregnancy. Paroxetine, in particular, has been identified by the FDA as being associated with a two fold increase in congenital heart disease (mostly atrial and ventricular septal abnormalities) if consumed in the first trimester.[38] FDA labeling of antidepressant drugs is the cause of ongoing controversy (see www.fda.gov/ohrms/dockets/dailys/04/sep04/092304/04n-0338-c00001-vol1.pdf).

Monoamine oxidase inhibitors (MAOIs)

As with other psychoactive drugs, there is little in the obstetric anesthesia literature about these agents. It is well known that first generation MAOIs, which bind irreversibly to both A and B subtypes of monoamine oxidase (MAO), can produce lethal excitatory or depressive interactions with meperidine.[39,40] The former interaction, called type I, is thought to be the result of serotoninergic activity and is characterized by agitation, headache, rigidity, hyperthermia, convulsion, and coma. Meperidine is thought to be the only common opioid to elicit such a reaction. Type II is depressive, characterized by hypotension, respiratory depression, and coma.

Table 20.4 Causes of death in serotonin syndrome

1. Rhabdomyolysis
2. Disseminated intravascular coagulation
3. Respiratory distress syndrome
4. Cardiovascular collapse

Monoamine oxidase inhibitors are known teratogens in animals, but their effects in humans are unclear. Importantly for anesthesiologists, severe hypertension may also follow administration of indirect-acting pressor agents, such as ephedrine and metaraminol.[41] Treatment with MAOIs leads to accumulation of norepinephrine in sympathetic nerve terminals, and indirect-acting agents can release large quantities of this and other transmitters. Thus, an exaggerated hypertensive response may ensue, and vigorous α-adrenoreceptor blockade (e.g. with phentolamine)[42] may be required. Infusions of direct-acting agents such as epinephrine are preferred for maintenance of blood pressure, despite concerns in respect of uterine artery constriction. Caution is needed because receptor hypersensitivity may develop in these patients.[43]

A case report[44] describes the use of opioid- and epinephrine-free epidural analgesia for labor in a woman who had consistently used phenelzine, a first-generation MAOI, for six years. Careful establishment of regional blockade obviated the need to administer vasopressors. Invasive arterial monitoring was instituted once the decision was made to proceed to C/S. Fentanyl had been used uneventfully for two general anesthetics in the past, but it was not needed for this delivery. Epidural morphine provided postoperative analgesia without incident and the newborn appeared normal.

Monoamine oxidase inhibitors inhibit degradation of serotonin, whereas SSRIs and TCAs inhibit serotonin reuptake. When combined, there is a synergistic effect, which produces a hyperserotoninergic state, most commonly as a result of concurrent or temporally related consumption of MAOI and SSRI. This is rare but occasionally leads to death from rhabdomyolysis, disseminated intravascular coagulation, adult respiratory distress syndrome, and cardiovascular collapse (see Table 20.4).[45] Secondary effects of the hyperthermia that follows the centrally mediated muscle rigidity have been successfully treated with muscle relaxation, sedation, and controlled ventilation.[35]

Second-generation MAOIs inhibit only the A subtype of MAO. Their pharmacology was reviewed by McFarlane.[46] Moclobemide is one drug in this group and is classified as a reversible selective inhibitor of monoamine oxidase A. Its efficacy seems comparable to that of SSRIs, with one study suggesting rapid improvement in quality of life and social functioning.[47] No important interactions with TCAs are reported but animal work suggests that meperidine is contraindicated.[48] There is also the potential for prolongation or enhancement of analgesics and anesthetic induction agents.[46]

Electroconvulsive therapy

Electroconvulsive therapy (ECT, electroshock) is a historically important and highly effective form of treatment in psychiatric practice. It is particularly useful where psychotropic medication has failed or when urgent control of an illness is required. Suicidal or violent patients (see earlier), or those whose condition poses a threat to their life (e.g. the catatonic or profoundly depressed may refuse to eat or drink) can improve rapidly with ECT. Pregnant patients may need ECT for urgent control of symptoms, with implications for the anesthesiologist. Two reviews[49,50] attest to the efficacy and relative safety of the practice, which has the added advantage that psychotropic medication can be minimized or avoided. Its mechanism of action is unclear, but ECT is thought to increase levels of neurotransmitters more rapidly than is possible with oral therapy. For certain delusional patients, ECT may be seen as punishment.

The practice of inducing convulsions was begun by von Meduna[51] following the shrewd observation that epileptic patients rarely developed schizophrenia. It was known that psychiatric patients became briefly asymptomatic after a seizure, regardless of its cause. Initial attempts to produce seizure activity involved i.v. injections of pentylenetetrazol (Metrazol). It was some years, however, before a reliable means of inducing convulsions was devised by Cerletti.[52]

The earliest ECT was quite barbaric, with serious fractures and other injuries following the unmodified convulsions. Interestingly, the only subset to improve were the depressed schizophrenics, whose mood improved; the schizophrenia was unaffected. General anesthesia of short duration has made the experience safer and more pleasant. Current practice includes establishment of i.v. access, preoxygenation, induction of anesthesia with methohexital and a small dose of succinylcholine (e.g. 0.5 mg/kg) to modify the peripheral expression of the seizure.

The first use of ECT in pregnancy was inadvertent. A psychotic patient was known to have an abdominal mass, but the fact that this was a gravid uterus was not appreciated until later. The pregnancy went to term and the child was developmentally normal.[53] A literature review[50] uncovered 300 case reports over the period 1942–91. Complications occurred in 28 cases – 5 in the first trimester, 11 in the second, 8 in the third, and the remainder at unspecified times. Fetal dysrhythmias occurred in five cases but were evanescent. One woman who received a total of 35 courses of ECT delivered prematurely. Five instances of vaginal bleeding following treatment were reported in this series. One of these was thought to represent recurrent mild abruptio placentae, because there was associated transient hypertension with each course. A large retroplacental clot was found at C/S at 37 weeks' gestation when vaginal bleeding began during labor.[54] Postictal uterine contractions were noted for a brief time in two women, and four others went on to develop premature labor.

The review points out the areas of principal concern for the anesthesiologist, namely aortocaval compression, fetal hypoxia, pulmonary aspiration, and specific drugs for anesthesia. Recommendations for ECT during pregnancy are in Table 20.5.

Thiopental is safe in pregnancy but its potent anticonvulsant activity makes it less desirable. Methohexital, with a shorter duration of action and propensity for excitatory phenomena, is a better drug. Regardless of agent, rapid sequence induction with cricoid pressure and tracheal intubation are mandatory after the first trimester to protect the airway. Similarly, lateral uterine displacement should be instituted from about 20 weeks' gestation, using a wedge under the right hip. Hyperventilation with 100% oxygen prior to ECT may enhance the quality of the seizure, but severe respiratory alkalosis must be avoided.[50] Uterine contractions and FHR must be monitored before and after ECT, and the woman must be observed for vaginal bleeding after the convulsion. Provided that all precautions are taken, ECT is usually safe in pregnancy; however, one report describes status epilepticus following ECT in a woman at 22 weeks' gestation which led to multiorgan failure and fetal demise. The decision to embark on ECT treatments is clearly one to be made in consultation with the obstetrician, psychiatrist, and anesthesiologist.[55]

Table 20.5 Anesthetic considerations for electroconvulsive therapy in pregnancy

1. Cease anticholinergic medication
2. Monitor uterine contractions
3. Rehydrate
4. Sodium citrate
5. Lateral uterine displacement after 20 weeks' gestation
6. Fetal monitoring after 20 weeks' gestation
7. Tracheal intubation after first trimester
8. Normocapnia
9. Observe for contractions and bleeding post-ECT

Panic disorder

This disorder, first described by Klein in 1964, is characterized by: (1) sudden, spontaneous, unexpected feelings of terror and anxiety; (2) autonomic equivalence of anxiety; (3) desire to flee the situation and return to a safe place; and (4) phobic avoidance of the places where such attacks occur.[56]

This sometimes disabling syndrome often begins in the third decade, when many women conceive. Interestingly, some find that their symptoms improve during pregnancy.[57] Attacks typically take place in restaurants, crowded stores, supermarkets, and on public transport. Besides the distress of the attack itself, it is possible to develop anticipatory anxiety about having another episode. Furthermore, phobic avoidance may develop for the place or places where attacks have occurred; sufferers with severe disease rarely leave home for years. An increased incidence of this disorder is seen in first-degree relatives of sufferers.[58] Attempts at self-medication can lead to abuse of both alcohol and sedative drugs, while the risk of suicide approaches that for patients with a major depressive illness.[59]

Drug therapy

Cognitive–behavioral therapy is commonly employed in the management of this condition, but it is pharmacotherapy that

Table 20.6 Recommendations for benzodiazepine use during pregnancy

1. Before conception, carefully reevaluate pharmacotherapeutic regimens.
2. Taper the dose of benzodiazepines so that breakthrough symptoms of panic and/or withdrawal are avoided.
3. For patients on short-acting agents (e.g. alprazolam) who develop recurrence, consider adding a tricyclic antidepressant.
4. Consider switching patients on alprazolam to clonazepam, which has a longer half-life and may decrease the incidence of rebound anxiety.

most affects the patient seen by the obstetric anesthesiologist. Selective serotonin reuptake inhibitors and TCAs are often used and are discussed earlier. The MAOIs may succeed when other antidepressants fail, but there are no data to date concerning second-generation drugs (e.g. moclobemide). Phenelzine is very effective.[60] Commonly prescribed drugs are benzodiazepines (BZD), particularly alprazolam and clonazepam. Benzodiazepines act by mimicking both the principal inhibitory neurotransmitter in the brain, γ-aminobutyric acid (GABA), and glycine, the major inhibitory transmitter in the spinal cord and brain stem.

Benzodiazepines are potentially harmful to the fetus, although evidence from studies is scarce. Exposure to BZD in the first four months of pregnancy does not significantly increase the risk of oral clefting, as determined by a case-control study.[61] Recommendations for BZD use in pregnancy are summarized in Table 20.6.

Nonpharmacologic treatment, such as cognitive–behavioral therapy, should be first-line treatment in pregnant women with generalized anxiety disorder, or panic disorder.[62]

In December 1991, the Upjohn voluntary reporting system database had on file > 900 cases in which in-utero exposure to alprazolam had occurred. There were six reports of apparent BZD neonatal withdrawal, characterized by irritability, hypertonia, sweating, brisk reflexes, and excessive crying.[6] Diazepam, a common BZD, can produce the "floppy infant syndrome" even when its use is confined to the management of labor. The features of this syndrome include hypotonia, poor temperature regulation, poor Apgar score, and failure to feed.[63] Conventional practice for management of labor does not include diazepam, except perhaps in the early treatment of seizure activity.

Anesthetic implications

Pregnant patients with panic disorder are encountered rarely, but they may present management problems. If maintained on BZD, they are likely to be tolerant of other drugs in that class, but interactions may occur. The central sedative properties may potentiate those of epidural opioids, whereas the GABA-ergic activity may lower the pain threshold. The patient in labor who has an attack may wish to flee but may be constrained by monitors, infusions, epidural lines, and other pieces of apparatus. Sympathetic support is called for, perhaps with pharmacologic assistance. Short-acting BZDs in small doses may help (e.g. i.v. midazolam, one-milligram boluses until control is achieved). Clonidine, which is a useful epidural analgesic may be worth trying as an i.v. anxiolytic in doses of 25 μg. Sedation is likely once 100 μg is exceeded, although much larger doses have been used for control of hypertension in pregnancy. Clonidine is safe in pregnancy with no harmful neonatal effects.[64] Addition of clonidine to the epidural solution might achieve improved analgesia and useful sedation simultaneously.

Conclusion

Personality disorders, mood disorders, schizophrenia, and adjustment disorders constitute the bulk of the psychiatric syndromes likely to present to the obstetric anesthesiologist. Many of the patients with these conditions will be on medications that may interact to a degree with anesthetic and analgesic agents. In addition, the women themselves can be challenging in view of their abnormal psychology, complicated further by the stress of pregnancy, the pain of labor, and the distress that can accompany the difficult decisions that often need to be made.

An even more difficult challenge is the patient with a psychotic illness, control of which may be affected adversely by pregnancy. Consultation with the obstetrician and, importantly, attending psychiatrist, is necessary if the illness is to be understood fully. After consultation, it is possible to devise a plan for safe conduct of anesthesia and analgesia. It is important to seek psychiatric advice on the best approach to each individual patient.[65] Not all anesthesiologists are skilled in this area, and time spent in consultation before entering the labor suite may be invaluable.

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21 MALIGNANCY AND PREGNANCY

Holly A. Muir, Michael Smith, and David R. Gambling

Introduction

Malignancy complicates between 0.02% and 0.10% of all pregnancies and in one study cancer diagnosis was associated with 1 in 1000 deliveries.[1] Pregnancy does not affect the frequency of cancers seen in women of childbearing age. Melanoma may be the most frequent malignancy seen during pregnancy (1:350), followed by cervical cancer (1:2250), Hodgkin lymphoma (1:3000), breast cancer (1:7500), ovarian cancer (1:18 000), and leukemia (1:75 000).[2] However, the National Cancer Institute maintains that breast cancer is the most common cancer seen in pregnant and postpartum women at 1:3000 pregnancies (www.cancer.gov/cancertopics/pdq/treatment/breast-cancer-and-pregnancy).

In general, the prognosis for pregnant women with malignant lesions is the same, stage for stage, as for nonpregnant women. However, for many reasons, diagnosis of cancer during pregnancy occurs at more advanced stages of the disease.

Typically, during pregnancy, what benefits the mother also benefits the fetus. However, that is not true in the case of the pregnant woman with cancer as treating the cancer often means compromising the pregnancy. Depending on the type of cancer and gestational age at diagnosis, treatment can sometimes be delayed until the fetus is either viable or mature. In some cases, protection of maternal and fetal health are congruent, but when care of the mother imposes iatrogenic risk to the fetus, the mother may decide to delay or alter her treatment for the good of the fetus, potentially to her own detriment.

Fetal monitoring

Fetal and uterine monitoring during cancer surgery is controversial. Though steps can be taken to improve uterine perfusion and fetal oxygenation if they appear compromised during surgery, monitoring may be impractical in emergent or urgent situations, and requires expertise often not possessed by anesthesia personnel. Indeed, fetal monitoring has not been documented to improve fetal outcome[3] and misinterpretation of the fetal tracing could lead to unnecessary or even unsafe interventions. Although uterine activity monitoring is not considered a necessity for the intraoperative management of most pregnant surgical patients, preoperative and postoperative monitoring of uterine activity and fetal heart rate is advocated and tocolysis may be used if uterine activity increases.

Breast cancer

Epidemiology

Breast cancer affects 1 of every 3000–7500 pregnancies.[2,4] Because it is more common in women of advanced age, and because there is a current tendency toward delaying childbirth, breast cancer during pregnancy is expected to become more common.[4] Two to five percent of all breast cancers present during pregnancy.[5,6] One group estimated that 4500 cases are diagnosed annually in the USA.[7] In women younger than 45 years of age with a breast carcinoma, 7.3% are pregnant or lactating.[4] The majority of breast cancers diagnosed in pregnancy are infiltrating ductal carcinoma.

Signs and symptoms

Breast cancer during pregnancy is difficult to diagnose because of changes to breast tissue during pregnancy. Ninety percent of pregnancy-associated breast cancers are diagnosed after self-examination of a painless mass,[5] but diagnosis often is delayed as the patient and/or her physician may be uncomfortable with breast examination during pregnancy. As a result, women tend to present with more advanced disease.[6] Indications for mammography, core biopsy, and open biopsy are the same for pregnant and nonpregnant women. Mammography has limited sensitivity in pregnancy because of changes in radiographic density and it requires shielding to minimize fetal exposure. Identification of a mass is followed with fine-needle aspiration or open biopsy. Fine-needle aspiration has a reported sensitivity and specificity of 94% and is widely used to provide a diagnosis.[8] Excisional biopsy can be performed under local anesthesia to minimize fetal anesthetic exposure.

Treatment

The treatment plan for a pregnant woman with breast cancer needs to consider the stage of the malignancy and maturity of the fetus. For stage I and operable stage II (localized breast cancer), the treatment of choice in pregnancy is modified radical mastectomy.[5] A second choice is total tumor excision and axillary node dissection to be followed by whole breast irradiation after delivery. Breast-conserving surgery requires an unacceptably large dose of radiation for the fetus. However, if the cancer is diagnosed late in pregnancy, radiation can be delayed until after delivery of the baby.

For stage III and stage IV disease (locally advanced or metastatic breast cancer), chemotherapy and radiation should be considered in pregnant women as it would for nonpregnant women. Breast cancer is most often treated in a multimodal fashion utilizing surgery, radiation, and chemotherapy. During pregnancy, when radiation therapy is relatively contraindicated, the other two modalities need to be adjusted. Chemotherapy has been used without harm to the fetus. Termination of pregnancy is not

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recommended prior to chemotherapy in the second or third trimesters.

The National Comprehensive Cancer Network has recently released practice guidelines for the treatment of breast cancer during pregnancy (see Figure 21.1).[9,]

Prognosis

Although pregnancy-associated breast cancer is diagnosed more often in advanced stages, patient age and stage-matched prognosis is the same as in nonpregnant women.[5] The five- and ten-year survival rates of pregnant women with breast cancer are identical to those of nonpregnant women.[10] Babies born to women with breast cancer tend to have lower birth weights.[5,]

Anesthetic implications

Anesthetic management must take into account the side effects of chemotherapeutic agents, if used (see Table 21.1). Reported complications include severe diffuse brachial plexus pathology following interscalene blockade in patients receiving cisplatin,[11] and prolonged neuromuscular block from succinylcholine in patients treated with alkylating chemotherapeutic drugs.[12]

Breast cancer can metastasize via the bloodstream to affect virtually any organ of the body. Dissemination most often is found in the lung, bones, liver, adrenals, brain, and meninges. Bone pain and pathologic fractures should be considered when selecting regional anesthesia and during positioning. Caution must be taken during neuraxial anesthesia due to the risk of metastatic disease to the spine or unmasking symptoms in women with spinal tumors. Obstruction of the superior vena cava (SVC) by spread of cancer into the mediastinum may cause airway obstruction in a pregnant patient with metastases. One parturient with SVC obstruction delivered uneventfully by cesarean section (C/S) under epidural anesthesia.[13]

Correction of electrolyte abnormalities, nutrient deficiencies, anemia, and coagulopathy may be needed. Hepatic or renal dysfunction may influence the choice of anesthetic drugs.

Surgical resection for breast tumors has been done successfully under cervical epidural block, thoracic paravertebral block, and

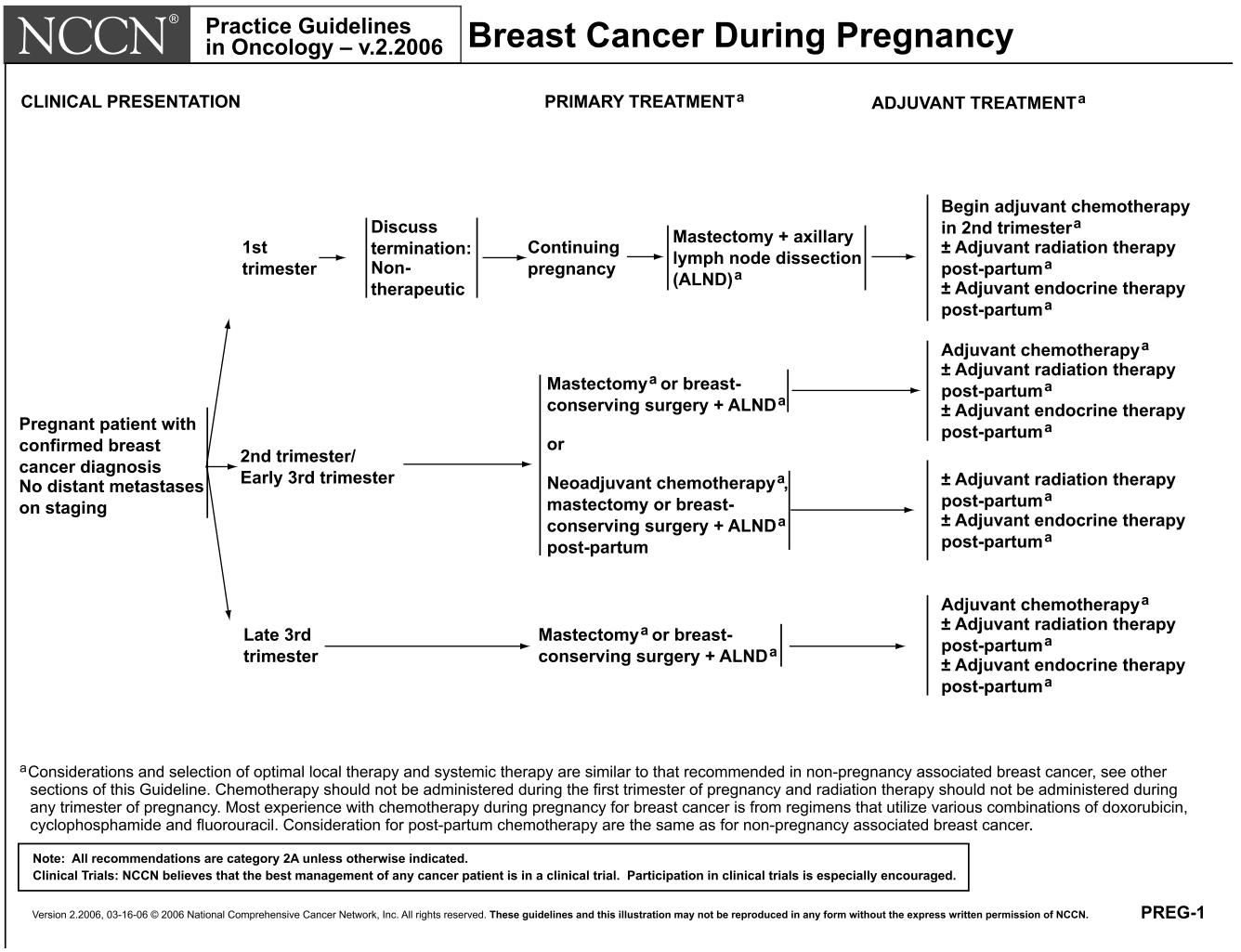

Figure 21.1 Practice guidelines for the treatment of breast cancer during pregnancy (with permission).

Table 21.1 Side effects of chemotherapeutic agents

Nausea and vomiting
Diarrhea and constipation
Anemia
Malnutrition
Memory loss
Depression of the immune system, infection, and sepsis
Hemorrhage
Secondary neoplasms
Cardiotoxicity
Hepatotoxicity
Nephrotoxicity
Ototoxicity

With large tumors, such as large lymphomas, some patients develop tumor lysis syndrome from the rapid breakdown of malignant cells. Although prophylaxis is available and is often initiated in patients with large tumors, this is a dangerous side effect, which can lead to death if untreated.

A proportion of patients report fatigue or nonspecific problems, such as inability to concentrate; this is sometimes called post-chemotherapy cognitive impairment.

Specific chemotherapeutic agents are associated with organ-specific toxicities, including cardiovascular disease (e.g. doxorubicin), interstitial lung disease (e.g. bleomycin) and occasionally secondary cancer (e.g. MOPP therapy for Hodgkin disease).

general anesthesia.[14] Regional anesthesia may reduce fetal drug exposure and maternal risks.

Cervical cancer

Epidemiology

The reported incidence of cervical cancer during pregnancy varies depending upon the report. Some authors consider different degrees of invasiveness while others deem carcinomas after a recent pregnancy as being pregnancy related. Overall, approximately, 0.02% to 0.40% of pregnancies are associated with cervical cancer and 0.5% to 3.0% of invasive cervical cancers are complicated by pregnancy.[15,]

Signs and symptoms

The presentation of cervical cancer depends on the extent of the disease. Most women with cervical cancer are asymptomatic and are diagnosed with abnormal cytology on routine Papanicolaou (Pap) screening.[7] In one study, pregnant patients were 63% more likely to be diagnosed using Pap smear than nonpregnant matched cases who presented with abnormal bleeding.[16] The Pap smear may have higher rates of false positive and negative tests during pregnancy.[15]

Vaginal bleeding is the most common symptom of carcinoma of the cervix in pregnancy, thus vaginal bleeding during pregnancy requires evaluation of the cervix.

Treatment

Women in early pregnancy (<24 weeks' gestation), with intraepithelial or microinvasive cervical cancer, can be treated with cold knife conization and large loop excision but the risks of preterm labor, low birthweight and cesarean section are increased, more so after large loop excision.[17]

Some physicians consider delaying treatment in women with early stage cervical cancer. However, these women should receive complete evaluation, including laparoscopic lymphadenectomy, before delaying treatment.[18]

Although radical hysterectomy has been the usual therapy for cervical cancer in pregnancy, one group looked at delaying therapy in patients with stage Ia or Ib cervical cancer to optimize fetal outcome. The mean diagnosis to therapy interval was 144 days for those who delayed versus 17 days for those who did not delay treatment. Fetal outcome was good in the delayed group, and at two-year follow-up, all patients were tumor free.[19]

Others have reported a fertility-preserving surgery (abdominal radical trachelectomy) for young women with cervical cancer during pregnancy.[20] There has been at least one case describing a successful pregnancy following radical trachelectomy, using ovum donation and in vitro fertilization.[21]

Prognosis

Comparing 44 pregnant women diagnosed with all stages of cervical cancer to matched nonpregnant controls, van der Vange found similar survival rates (80%) using standard treatment.[22]

Anesthetic implications

Anesthesiologists should consider the effects of treatment with chemotherapeutic agents as well as dealing with a patient who is potentially immunocompromized. Invasive monitoring and regional anesthesia should be performed using strict asepsis. Most patients with stage IV cancer have local extension of tumor into the urinary system and may present with renal failure. Patients with advanced disease may be anemic from chronic disease and malnutrition. However, most patients with early cervical cancer will not present any major anesthetic problems. If laparoscopy is required, present evidence suggests that laparoscopic surgery in pregnancy is a safe option. Left uterine displacement, maintaining end-tidal carbon dioxide between 32–34 mmHg and maternal blood pressures within 20% of baseline, and limiting abdominal insufflation pressure to 8–15 mmHg are important factors to remember.[23]

Ovarian cancer

Epidemiology

Ovarian malignancies are rare during pregnancy and are associated with favorable maternal and neonatal outcomes because most are diagnosed at an early stage.[24] Pregnancy and lactation suspend ovulation and, thus, are protective factors against

the development of ovarian malignancy.[25] Ovarian cancer can be divided into three categories: epithelial carcinoma, germ cell cancer, and stromal cancer. Germ cell cancer, the most common type of ovarian cancer associated with pregnancy, originates in cells destined for ovulation (egg cells). In one report an adnexal mass of ≥5 cm was diagnosed by ultrasound in 0.05% of deliveries.[26] The majority were dermoid cysts and only 0.0032% of deliveries were associated with an ovarian cancer.[26]

Signs and symptoms

Most tumors are found on routine ultrasound, but the patient may present with pain from torsion, rupture, and obstruction of labor.[27] Screening tests include measuring CA125 levels but these are not particularly sensitive. Elevation of CA125 in the serum is not specific to ovarian cancer and can be detected in malignancy of the fallopian tube, peritoneum, cervix, endometrium, breast, colon, and lung. However, CA125 may also be elevated in many benign conditions, including pregnancy, endometriosis, ovarian cysts, and cirrhosis. In addition, CA125 is elevated in only 40% to 50% of patients with stage I/II ovarian tumors.

Treatment

In general, women with malignant ovarian tumors should receive immediate optimal treatment regardless of the stage of pregnancy. Nonsuspicious adnexal masses are treated expectantly, but surgical intervention during pregnancy is indicated for large and/or symptomatic tumors and those that are suspicious of malignancy on imaging tests.[28] Treatment will depend on the size, type, and stage of the tumor. It may be managed with open or laparoscopic surgery, with adjuvant chemotherapy. One report states that irrespective of the stage of ovarian cancer, conservative surgery and adjuvant chemotherapy for women with malignant germ cell tumors achieves a favorable outcome in terms of survival and fertility, compared to radical surgery.[29] Various chemotherapeutic agents have been used successfully during pregnancy in the second and third trimester with minimal fetal toxicity.[30,31]

Prognosis

Epithelial ovarian cancer has a poor prognosis due mainly to the fact that 70% of the women are diagnosed at an advanced stage. In women with distant metastases, the five-year survival rates are only 10% to 30%. Survival rates for germ cell cancer treated with oophorectomy and chemotherapy are very good.

Anesthetic implications

Consideration of the impact from chemotherapeutic drugs is important, especially the association of cisplatin with peripheral nerve damage and the development of cardiovascular risk factors.[32] In patients with advanced disease, anemia and electrolyte imbalance may be present, and liver function should be evaluated preoperatively. Laparoscopy for resection of adnexal masses has been performed successfully during pregnancy using epidural, combined spinal–epidural, and general anesthesia.[33,34]

Endometrial cancer

Endometrial cancer and pregnancy are almost always noncompatible. There are only 24 cases of endometrial cancer in pregnancy reported in the literature[35] and most were detected during first trimester abortions. Five cases were associated with a live fetus and in two of these cases the diagnosis was made four months postpartum.

There are reports of successful pregnancies following conservative hysteroscopic removal of grade 1 endometrial carcinoma,[36,37] but others warn against such conservative management.[38]

Vulvar cancer

Epidemiology

Vulvar cancer is rare during pregnancy. The usual histologic types of vulvar cancer are squamous cell carcinoma followed by melanoma and verrucous carcinoma. It has been suggested that vulvar cancer exists as two separate diseases. The first type involves human papillomavirus infection, which predisposes the patient to vulvar cancer. The second type involves abnormal epithelial disorders and advanced age. Approximately 5% of vulvar cancer occurs during pregnancy and recurrence can occur quickly in the setting of pregnancy.[39]

Signs and symptoms

No features are diagnostic of vulvar cancer and diagnosis is based on biopsy alone. Therefore, biopsy must be performed on any suspicious lesions of the vulva, asymptomatic or symptomatic. Spread to the vulva from a cervical cancer must be ruled out.

Treatment

Early surgical treatment is mandatory and consists of radical or modified radical vulvectomy often with bilateral groin dissection (depending on the original histology).[40] Postdelivery radiotherapy may be required.

Prognosis

The prognosis of patients with vulvar cancer is generally good. The overall five-year survival is 70% and correlates with the stage of disease and lymph node status.[40]

Anesthetic implications

Biopsy can be done under local anesthetic with or without intravenous (i.v.) sedation. Surgical resection is best performed under spinal anesthesia and spinal opioids will reduce the severity of postoperative discomfort.

Head and neck cancers

Epidemiology

Thyroid carcinoma is one of the most common head and neck cancers in women of reproductive age. In one report thyroid cancer is rated the third most common cancer diagnosed during pregnancy.[41] In a case series of 15 women with differentiated thyroid carcinoma during pregnancy, 93% were in stage I, 93% had papillary thyroid carcinoma, and 60% were diagnosed in the first trimester at the first antenatal visit.[42]

Cancers of the larynx, maxilla, oropharyngeal cavity, thyroid, and parathyroid have been reported during pregnancy, but oral and oropharyngeal cancer is rare in reproductive age females and accounts for less than 2% of all cancers.[43]

Signs and symptoms

Thyroid nodules are common in adults. Most are benign; however, solitary nodules of the thyroid noticed during pregnancy are approximately three times more likely to be malignant compared with those in nonpregnant women of the same age.[44] Symptoms may include hoarseness, neck pain, and enlarged lymph nodes. Oral and nasopharyngeal cancers are diagnosed by biopsy of suspicious lesions and most often present as a chronic nonhealing wound. Laryngeal cancer may present as chronic cough, hoarseness, stridor, or respiratory distress.

Treatment and prognosis

In most cases, termination of pregnancy is not recommended. Thyroidectomy can be performed in the second trimester if the diagnosis is made in the first trimester, and deferred until after delivery, if the diagnosis is made later. Radioiodine and thyroid-stimulating hormone suppression may be required after delivery. In one report, pregnancy had no effect on mortality.[45] Thyroid cancer has a high cure rate with ten-year survival rates for all patients with papillary thyroid cancer estimated at 80–90%. Cervical metastases are present in 50% of small tumors and in over 75% of larger thyroid cancers. Distant metastases are uncommon, but lung and bone are common sites. Tumors that invade or extend beyond the thyroid capsule have a high local recurrence rate.

Cancer of the larynx is treated with surgery, radiotherapy, or a combination depending on the stage of disease, histologic type of disease, and age of the patient. Surgery with immediate reconstruction is the treatment of choice for oropharyngeal cancer. Postoperative radiotherapy is occasionally needed. Nasopharyngeal cancer is very responsive to a variety of chemotherapeutic agents and radiotherapy can be administered with abdominal shielding to minimize exposure to the fetus. Prognosis for small laryngeal cancers that have not spread to lymph nodes is very good, with cure rates of 75% to 95% depending on the site, tumor bulk, and degree of infiltration.[46] Mouth and tongue cancer are often well advanced at the time of diagnosis, and have metastasized beyond the oral cavity. If metastasis has occurred, the prognosis for oral cavity cancer is poor. The overall five-year survival rate for mouth cancer is 55%, a statistic that has not improved in 30 years.

Anesthetic implications

Any patient with a history of head and neck cancer should be considered as having a possible difficult airway. Radiotherapy and previous surgery can alter anatomy, tissue compliance, and vascularity, making visualization during direct laryngoscopy difficult. Radiation can make tissues friable and care must be taken during placement of nasal endotracheal tubes, esophageal stethoscopes, and orogastric/nasogastric tubes.

Central nervous system (CNS) tumors (also see Chapter 9)

Epidemiology

The incidence of malignant brain tumors complicating pregnancy is 3 per 10 000.[47] Although rare, brain tumors during pregnancy carry the potential for maternal and fetal demise. The incidence of choriocarcinoma after a term pregnancy is 0.2 per 10 000, with brain metastases occurring in 14–28% of cases.[47] There is no particular type of primary brain tumor specifically associated with pregnancy. The distribution of primary CNS tumors in pregnancy is similar to nonpregnant women, with gliomas representing the majority of symptomatic neoplasms, followed by meningiomas and acoustic neuromas.[48]

Signs and symptoms

Symptoms represent a rapidly escalating neurologic crisis and usually result from increased intracranial pressure (ICP). Headache is the initial presenting symptom in the majority of those with brain tumors, and intractable nausea and vomiting may be difficult to differentiate from morning sickness. Gait disturbance, seizures, urinary incontinence, memory loss, and paralysis have been reported. Patients are likely to present initially when the intravascular fluid volume peaks in the latter half of the second trimester, a time when the fetus may be viable but premature. Magnetic resonance imaging (MRI) is the preferred method to establish a diagnosis providing excellent soft tissue resolution while avoiding fetal exposure to ionizing radiation.

Treatment

Treatment for CNS tumors during pregnancy depends on the type and grade of the malignancy, the woman's clinical condition, and the stage of pregnancy. Most low-grade, slow-growing tumors can be followed by neuroimaging, with treatment deferred until after delivery. Corticosteroids and anticonvulsants help to alleviate symptoms until fetal maturity. High-grade gliomas or a tumor associated with continued clinical deterioration require prompt surgical resection regardless of gestational age.

Radiation therapy and chemotherapy are commonly used as an adjuvant therapy after resection of many CNS tumors. Cranial

radiation therapy with abdominal shielding in the late stages of pregnancy is not associated with an increased risk of birth defects or fetal loss, but carries an increased risk of childhood leukemia.[48]

Prognosis

Overall, prognosis depends on the type of CNS malignancy and the grade of disease. Patients with low-grade astrocytomas have a five-year survival rate of 50%, while survival rates of low-grade oligodendrogliomas approach 30% at ten years.[48] Prognosis for high-grade gliomas is poor, with a median survival for glioblastoma multiforme of one year. The five-year survival rate of patients with meningiomas is 90%.

Anesthetic implications

Management must be a collaborative effort by all physicians involved, and each patient must be assessed individually to determine an optimal anesthetic plan. Patients who present at term should receive corticosteroids to reduce cerebral edema and then be delivered expeditiously.[47] Induction of labor is not appropriate in neurologically unstable patients with threatened herniation, but may be appropriate in more stable patients. Anticonvulsant levels need to be closely monitored in the pregnant patient because changes in serum binding proteins, albumin, and circulating blood volume can change the levels of active drug.

Successful anesthesia for craniotomy in the sitting and supine positions during pregnancy has been reported without adverse maternal or fetal outcome.[49,50] Care must be taken to maintain cerebral perfusion pressure and strategies enlisted to decrease cerebral blood flow and ICP while maintaining placental blood flow. Fetal monitoring is controversial but may prove useful as a monitor for overall organ perfusion. Excessive hydration with intravenous fluids and hyperglycemia should be avoided.

Epidural anesthesia is generally contraindicated in patients with increased ICP due to the risk of inadvertent lumbar puncture and catastrophic brain stem herniation. Cesarean delivery under general anesthesia is recommended for patients with significant mass-occupying lesions as many of these patients are confused and uncooperative.[51] When neuraxial anesthesia is considered for C/S in women with a brain tumor and normal ICP, the potential for primary or metastatic disease of the spine and the woman's coagulation status must be evaluated.

Trophoblastic disease

Epidemiology

Gestational trophoblastic disease (GTD) describes a group of uncommon but interrelated clinical conditions derived from placental trophoblasts. Gestational trophoblastic disease includes hydatidiform mole and gestational trophoblastic neoplasia (GTN).[52] The term GTN is reserved for cases with persistent elevation of human chorionic gonadotropin (hCG) titers after evacuation of hydatidiform mole, metastatic disease, or choriocarcinoma. The incidence of hydatidiform mole is about 1 per 1000 pregnancies in most parts of the world. Choriocarcinoma is much less common, and estimates of the incidence are highly variable.

There is a strong ethnic difference in the incidence of GTD[53] with molar pregnancy three times higher in Japan than in Europe or North America. Higher rates of GTD are also reported among nonwhite Hispanic, American Indian, Eskimo, and Asian populations.[53]

The risk of GTD appears to be increased in patients with a previous molar pregnancy, and a partial mole with the coexistence of a fetus is rare. A twin pregnancy consisting of a complete hydatidiform mole and coexisting fetus (CHAF) is very rare. It differs from a partial mole in that there are two separate conceptuses, with a normal fetus and placenta comprising one twin and a complete molar gestation comprising the other.[54,]

Signs and symptoms

A complete hydatidiform mole presents with irregular vaginal bleeding between the sixth and the sixteenth week of pregnancy.[55] Abnormal abdominal swelling, hyperemesis, fatigue, and dyspnea are frequently observed. Symptoms of partial hydatidiform moles are less severe than those of complete moles. The diagnosis is made by ultrasound and elevated serum hCG levels.

Treatment

Most women with GTD are cured by surgical evacuation using suction curettage. The indications for initiating chemotherapy are: (1) evidence of metastases in the brain, liver or gastrointestinal tract, or radiological opacities larger than 2 cm on chest radiograph; (2) histological evidence of choriocarcinoma; (3) rising hCG titers.[56]

Treatment is tailored according to recognized adverse prognostic features. There are a variety of systems used to classify patients into low, intermediate, or high risk. The most commonly accepted system is to combine the International Federation of Gynecology and Obstetrics (FIGO) anatomic staging with the modified World Health Organization risk factor scoring system (see Tables 21.2 and 21.3).[57,58]

Low-risk patients are treated with single agent chemotherapy. Single agent methotrexate, actinomycin D, and etoposide have all

Table 21.2 FIGO staging

Stage I	Gestational trophoblastic tumors strictly confined to the uterine corpus.
Stage II	Gestational trophoblastic tumors extending to the adnexa or to the vagina, but limited to the genital structures.
Stage III	Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement.
Stage IV	All other metastatic sites.

From Benedet *et al.*, 2000[58]

Table 21.3 World Health Organization risk factor scoring

Prognostic factor	0	1	2	4
Age	<35	>35		
Prior pregnancy	mole	abortion	term	
Interval	<4 months	4–6 months	7–12 months	>12 months
Serum B-HCG	<1000	<10 000	<100 000	>100 000
ABO blood group maternal x paternal		OxA, AxO	B, AB	
Size of largest tumor			3–5 cm	>5 cm
Number of metastases		1–4	4–8	>8
Prior chemotherapy			single agent	multiple

Total score: 0–4 low risk, 5–7 intermediate risk, >8 high risk for death.
From Benedet *et al.*, 2000[58]

been shown to be effective. Because of its efficacy and safety profile, low-dose methotrexate, with folic acid rescue, remains the most widely used therapy for low-risk patients.[56] Actinomycin D, etoposide, and cyclophosphamide may be added in patients who develop methotrexate resistance.

In high-risk patients, multidrug regimens have been developed. Etoposide, methotrexate, and actinomycin D, alternating weekly with cyclophosphamide and vincristine (EMA-CO), is one recommended multidrug treatment. However, the best combination chemotherapy regimen for high-risk GTN requires further study.[59] The majority of patients are cured with chemotherapy. Patients with CNS metastases should be treated concurrently with whole brain irradiation.

The majority of twin pregnancies with CHAF result in evacuation of the pregnancy immediately upon diagnosis. Indications for immediate evacuation of the pregnancy include the development of preeclampsia, intractable vaginal bleeding, hyperemesis gravidarum, hyperthyroidism, or evidence of trophoblastic embolization.

Prognosis

Overall the prognosis for gestational trophoblastic disease is very good. Cure rates in the high-risk category are as high as 82% after treatment with combination chemotherapy.[60]

However, the outcome for women presenting with metastases from GTD is poor.

Anesthetic implications

The patient's coagulation status should be assessed and blood count, electrolytes, blood gases, thyroid, hepatic and renal function, hCG, and chest x-ray should be reviewed. Preeclampsia may develop during the first or second trimester of a complete molar pregnancy, and affects about 25% of women with complete moles but only about 4% of women with partial moles. Hyperthyroidism occurs in about 7% of women with complete hydatidiform moles. Thyrotoxicosis, anemia, and dehydration due to bleeding may predispose to cardiac dysfunction and respiratory insufficiency. Perioperative management of thyrotoxicosis focuses on the control of sympathetic activity so that cardiovascular side effects are minimized. Uterine relaxation may increase blood loss and inhaled anesthetics with known tocolytic qualities should be used cautiously. Nitrous oxide, opioids, and muscle-relaxant agents may be preferred. Whereas general anesthesia is likely to be used for surgical evacuation of GTD, the use of spinal anesthesia has been described.[61]

A surveillance of metastatic disease should be done prior to any anesthetic. An invasive mole can penetrate the full thickness of the uterine wall and rupture, resulting in severe internal or vaginal bleeding. Invasive moles can also spread to other organs, most commonly to the vagina and the lung. Choriocarcinoma can spread virtually anywhere in the body but most commonly spreads to the lung, the lower genital tract, brain, liver, kidney, and the gastrointestinal tract.[62]

Interactions between chemotherapeutic agents and anesthetics should be reviewed in a woman who has received chemotherapy. Some concerns include hepatic and renal toxicity from methotrexate, an impaired stress reaction, and the risk of developing opportunistic infections.[12,63]

Lung cancer

Very few cases of lung cancer during pregnancy have been documented. One review of the literature found 35 cases of primary lung cancer associated with pregnancy.[64] The anesthetic technique was described in only 5 of 20 cases that required C/S (one spinal, three epidural, and one general anesthetic). In the same report, the authors describe a patient with metastatic lung cancer who underwent C/S for preterm twin delivery under spinal anesthesia with no adverse sequelae.[64] Lung cancer can metastasize to the placenta and the fetus as can other cancers such as melanoma, breast cancer, leukemia, lymphoma and sarcoma.[65]

Melanoma

The reader is referred to Chapter 19 for a review of malignant melanoma in pregnancy.

Hematological malignancies

The reader is referred to Chapter 17 for a more complete description of hematological cancers in pregnancy.

Summary

Although the diagnosis of cancer is always devastating, it is especially so in pregnancy.[66] However, the occurrence of cancer in pregnant women is not common but it has the potential to

provide multiple challenges for the anesthesiologist. An understanding of normal maternal–fetal physiology is critical in the diagnosis, surgical management, and postoperative care of pregnant women with coexisting malignancy.

Significant emotional issues also surround the care of these women. Physicians from different specialties should be involved in patient management, and a team approach that includes psychologic support is essential.

Despite the absence of strict guidelines, the goals of care should be to benefit the mother's life, treat curable malignant disease of pregnant women, try to protect the fetus and newborn from harmful effects of cancer treatment, and if possible retain the mother's reproductive system for future gestations.

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22 PREGNANCY AND TRANSPLANTATION

Kerri M. Robertson

Introduction

Transplantation is recognized as life saving for individuals suffering from end-stage organ failure. For many young women, improved transplant success rates and newer "obstetric-friendly" immunosuppressant drugs have allowed them the opportunity of achieving normal reproductive function, with the subsequent choice of childbearing. The most extensive experience with pregnancy in the posttransplant parturient has been in renal recipients with the first successful posttransplant pregnancy occurring in 1958.[1] Since then, thousands of successful deliveries have been reported in women after liver, heart, simultaneous kidney–pancreas and combined transplants (heart–lung(s), liver–kidney, liver–heart, and liver–lung). Despite the inherent increased risk to the mother and concerns about the effects of immunosuppressive drugs on fetal development, and the effects of pregnancy on transplant function, a successful outcome in such pregnancies is achievable. Consensus is that in the presence of good graft function and with stable maintenance immunosuppressive drug therapy, pregnancy is well tolerated, with most pregnancies resulting in successful outcomes for mother and newborn.[2,3,4,5] In addition, multiple pregnancies in a transplant recipient do not seem to increase the incidence of complications in the newborn or mother or augment graft dysfunction and failure.[6]

Statistics

Organ transplantation has become a relatively common surgical procedure performed in over 250 centers worldwide, with improvement in both patient and graft survival rates reported over the past two decades. As such, many of these recipients are healthy and live a relatively normal life, with an excellent chance of survival during and beyond their reproductive years. The National Transplantation Pregnancy Registry (NTPR), established in the US in 1991, is a voluntary reporting, retrospective database analyzing the long-term outcomes of female transplant recipients who have had pregnancies, graft function within two years of pregnancy, and the health of their offspring. The total number of pregnancies in female recipients reported to the registry as of January 2003 is shown in Table 22.1.[2] The number of outcomes exceeding pregnancies indicates multiple gestations.

In general, reports have not distinguished between recipients of transplants as adults and those who received transplants during childhood and adolescence. No information is available on pregnancy following small bowel transplantation.

Conception and pregnancy

Resumption of normal menstrual function and fertility may occur within weeks to months after transplantation with subsequent conception dependent on the recipient's pattern of episodes of rejection and infection and evidence of stable graft function. In addition, use of minimum immunosuppressive therapy with drugs developed after the introduction of cyclosporine A (CyA), may reduce the risk for delivery of low birthweight infants.[7] The incidence of prepregnancy hypertension, diabetes mellitus (DM), and renal insufficiency may also impact maternal and pregnancy outcome.[8] An understanding of the optimum criteria for consideration of pregnancy in transplant recipients and adherence to the recommended waiting period of at least one year following transplantation will alert the reader to those patients who, not satisfying these prerequisites, may anticipate a prohibitively high-risk antenatal and peripartum course (see Tables 22.2, 22.3, and 22.4).[3,4,5,9]

Despite good preconception and peripartum graft function and minimal morbidity from immunosuppressive therapy, life expectancy following transplantation is uncertain, and pregnancy should be considered as high risk. Collaborative interdisciplinary management between transplant specialists, obstetricians, perinatologists, and anesthesiologists is essential.

Issues that must be considered in every transplant parturient include: timing and mode of delivery; increased risk of preeclampsia; adverse effects of immunosuppressive drugs (hypertension, hyperglycemia, renal insufficiency), immunosuppressive drug levels and dosing; surveillance of graft function; maternal infection; residual physiologic alterations of end-stage organ disease; and coexisting disease effecting other organ systems.

Kidney and pancreas–kidney recipient

The age range of renal transplant patients who have completed successful pregnancies is 18 to 46 years.[7,10] Most studies conclude that pregnancy does not have an adverse long-term effect on patient survival or on renal graft function, if the glomerular filtration rate (GFR) is well preserved and the patient is normotensive.[10,11,12,13] Contrary to these findings, an estimated 12% of these women have been reported to develop new long-term medical problems following pregnancy, which doubles if uncontrolled hypertension, renal deterioration, or rejection occurs prior to 28 weeks' gestation.[14] It is uncertain whether such problems are pregnancy-induced or follow the natural time course for kidney recipients and graft survival.

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Table 22.1 NTPR: Pregnancies in all female transplant recipients (1991–2002)

Organ	Recipients	Pregnancies	Outcomes
Kidney	691	1058	1089
Liver	102	175	176
Liver–kidney	3	5	6
Pancreas–kidney	35	48	50
Heart	31	52	52
Heart–lung	3	3	3
Lung	13	14	14
Totals	878	1355	1390

Table 22.2 Criteria for consideration of pregnancy in kidney and pancreas–kidney transplant recipients

1. Good general health
2. Elapsed time from cadaveric transplant surgery 24 months, possibly one year for a living donor recipient, and <5 years from transplantation
3. Proteinuria <500 mg/24hr
4. Hypertension, if present, BP ≤140/90 mmHg on minimal drugs and easily controlled
5. No recent episodes of acute rejection in the preceding 6 to 12 months and no evidence of ongoing rejection
6. Mild renal dysfunction with a serum creatinine of less than 1.8 μmol/l (2 mg/dl) or preferably less than 1.25 μmol/l (1.5 mg/dl)
7. Stable maintenance level of immunosuppressive therapy:
   - Prednisone ≤15 mg/day
   - Azathioprine ≤2 mg/kg/day
   - Cyclosporine and tacrolimus at therapeutic levels
   - Mycophenolate mofetil and sirolimus are contraindicated and have to be stopped 6 weeks preconception
8. Normal graft ultrasound (absence of pelvicalyceal distension)
9. Rubella vaccine should be administered pretransplantation

Table 22.3 Criteria for consideration of pregnancy in liver transplant recipients

1. Pregnancy should be avoided for at least the first 6 months and preferably 9 to 12 months after transplantation
2. Evidence of stabilization of liver function and recovery from surgical complications
3. Completion of posttransplant prophylactic treatment of opportunistic infections, with no evidence of active viral infection
4. Maintenance immunosuppressive therapy
5. No evidence of acute rejection

Table 22.4 Criteria for consideration of pregnancy in heart and heart–lung transplant recipients

1. Pregnancy is generally not recommended in the first year after heart transplantation, and ideally not for two years posttransplant, to allow for recovery from primary and secondary disease processes
2. Asymptomatic, normal exercise tolerance, New York Heart Association Functional Class I
3. Well preserved ventricular function (echocardiography and cardiac catheterization)
4. No evidence of coronary atherosclerosis by angiography
5. Stable immunosuppressive regimen
6. No evidence of rejection on endomyocardial biopsy
7. Normal or near normal renal function

Table 22.5 Hallmarks of clinical rejection in the transplanted kidney

1. Fever
2. Diminishing urine output
3. Fluid retention
4. Hypertension
5. Worsening renal function (i.e. increased blood urea nitrogen, creatinine, beta-2 microglobulins)
6. Enlargement and tenderness of the ectopic kidney

Table 22.6 Causes of functional impairment of the transplanted kidney during pregnancy

1. Functional stress of pregnancy (glomerular hyperfiltration and sclerosis)
2. Accelerated progression of an underlying disease process
3. Preeclampsia
4. Cyclosporine A nephrotoxicity
5. Rejection (acute or chronic)
6. Hypertension

Adaptations of the kidney to pregnancy are paralleled by the denervated renal graft, although to a lesser degree. A sustained increase in GFR and renal plasma flow is seen in the first and second trimester, with a transient reduction of up to 30% during the third trimester and return to normal by 8 to 12 weeks postpartum, without permanent sequelae.[15] Proteinuria, frequently more than 500 mg/24 hours and as remarkable as 2–3 g/24 hours,[16] is seen in the third trimester in 30–40% of patients.[17] However, in the absence of hypertension or renal dysfunction, proteinuria is not significant and usually resolves postpartum.[18]

Rejection during pregnancy is a rare phenomenon but postpartum rejection and deterioration in renal function has been observed. There are no predictive risk factors for which patients will develop acute rejection and the diagnosis may be difficult (see Table 22.5). If deterioration in renal function occurs at any stage of pregnancy, treatable causes should be excluded (see Table 22.6). The impact of pregnancy on graft loss is difficult to evaluate. Recipients with graft dysfunction (serum creatinine >1.5 mg/dl) or rejection during pregnancy and the postpartum

period are more likely to deliver earlier as well as suffer eventual graft loss.[19,20]

Hypertension and preeclampsia are common and frequently severe. A blood pressure (BP) greater than 140/90 mmHg in the kidney transplant patient should be treated early and aggressively.[21] Maintaining a diastolic BP between 80–85 mmHg may preserve graft function and prevent the occurrence of a life-threatening hypertensive crisis or eclampsia. In general, hypertension, particularly before 28 weeks' gestation, is associated with adverse perinatal outcome.[22] Antihypertensive medications considered relatively safe during pregnancy include: α-methyldopa, beta-adrenergic antagonists, labetalol, clonidine, hydralazine, nifedipine, and diuretics.[8,10] Angiotensin-converting enzyme inhibitors should be discontinued because of potential adverse effects on the fetus, including oligohydramnios, pulmonary hypoplasia, and long-lasting neonatal anuria.[23] Delivery of the infant, regardless of gestational age, should be considered if the patient develops a hypertensive crisis, seizures, or diastolic BP over 110 mmHg, which is refractory to optimum therapy, and when no reversible aggravating factor can be found.[15] Due to the high incidence of hypertension in transplant patients, prophylactic low-dose aspirin has been proposed to decrease the incidence of preeclampsia.[24] There is an increased incidence of preeclampsia of 25–40%, compared with 8% in the nontransplant patient.[3,25,26] Diagnosis is difficult without a renal biopsy, because edema, proteinuria, hypertension, and increased serum uric acid levels may also indicate exacerbation of preexisting renal disease, drug toxicity, or acute rejection.[21] Abnormalities in the platelet count or liver function tests (LFTs) may be consistent with a diagnosis of preeclampsia, or immunosuppression-induced changes in an otherwise uncomplicated pregnancy.

The risk of bacterial infections of the genitourinary tract may be as high as 40%. Less frequently opportunistic viral and fungal infections may result from chronic immunosuppression and exposure to blood products during years on hemodialysis. Diagnosis and treatment is dictated by verification of infection with culture and sensitivity and/or serological monitoring, as uncommon organisms are frequently seen. Potential risks to the mother and fetus include: pulmonary, liver, and renal dysfunction, spontaneous abortion, intrauterine and perinatal infections, intrauterine growth restriction (IUGR), and preterm delivery. Cesarean section (C/S) is indicated if a cervical culture is positive for herpes simplex virus at term, as the incidence of neonatal infection resulting from vaginal delivery is at least 50%. With premature rupture of membranes, waiting for greater fetal maturity may not be desirable in view of this enhanced susceptibility to infection.

Causes of maternal death postpartum include infection, renal failure, uterine rupture, gastroenteritis, cerebrovascular and cardiac disease. Few deaths have been reported during or shortly after pregnancy: the majority occurring six to eight years later. In several small series, 5% to 30% of renal transplant recipient mothers died during their offspring's childhood.[10,27]

Residual physiologic alterations of end-stage renal disease (see Table 22.7) may have a potential negative impact on obstetrical outcome and vice versa. After kidney transplantation, persistent hypercalcemia due to hyperparathyroidism occurs in up to 20% of women, with the possibility of exacerbation at the beginning of the third trimester. This is associated with an increase in 1,25 dihydroxy vitamin D of placental origin.[28] Patients with moderate hypercalcemia (total serum calcium [Ca^{2+}] 11.5–13 mg/dl) have lethargy, and hypotension from polyuria and/or nausea and vomiting with hypovolemia. A total serum Ca^{2+} exceeding 14 mg/dl represents a medical emergency from hypertension, dysrhythmias, complete heart block, severe neuromyopathic symptoms, and renal failure.[29]

Table 22.7 Physiologic alterations in end-stage renal disease

Neurologic	• Central: lethargy, seizures, personality traits • Peripheral: sensory and motor neuropathy • Autonomic dysfunction
Respiratory	• Hypocarbia • Pleural effusion, edema, pneumonitis, infection
Cardiovascular	• Indeterminate volume status, susceptible to fluid overload • High cardiac output • Hypertension, left ventricular hypertrophy • Accelerated peripheral and coronary atherosclerosis • Tachycardia, dysrhythmias, and conduction disorders • Attenuated reactivity of the sympathetic nervous system • Reduced oxygen carrying capacity, increased peripheral extraction of O_2 • Pericarditis, cardiac tamponade
Endocrine	• Electrolyte disorders (hyperkalemia, hyperphosphatemia, hypermagnesemia, hypercalcemia, hyponatremia) • Metabolic acidosis • Secondary hyperparathyroidism • Glucose intolerance
Gastrointestinal	• Delayed gastric emptying and increased volume and acidity of gastric contents, aspiration risk
Musculoskeletal	• Osteodystrophy, muscle wasting
Hematologic	• Chronic anemia, right shift of hemoglobin dissociation curve • Platelet dysfunction, coagulopathy • Increased susceptibility to infection, carrier state for hepatitis B antigen and HIV • Reduced serum protein and abnormal binding • Decreased drug or metabolite clearance • Abnormal electrolyte and acid-base status • Altered permeability of the blood–brain barrier • Increased sensitivity to central nervous system depressants • Reduced serum cholinesterase level • Altered end-organ sensitivity or response or both
Altered drug effects	• Altered volume of distribution

Successful pregnancies have been reported in a number of kidney transplant patients with coexisting systemic disease, putting them at high risk, independent of transplant-related considerations. These coexisting conditions include: juvenile-onset DM, systemic lupus erythematosus, scleroderma, type 1 primary hyperoxaluria, sickle cell disease, Wegener syndrome, and Goodpasture syndrome.

In the kidney transplant recipient with juvenile-onset DM, there is a two fold increase in the pregnancy complication rate compared with recipients having other causes of chronic renal failure (CRF). This is likely related to the preexisting vascular complications seen with severe longstanding DM.[30,31,32] In addition, immunosuppression can increase the risk of infection, worsen diabetic control, accelerate vascular atherosclerotic disease, and increase rates of hypertension and thromboembolism. Bone fractures may be associated with steroid-induced osteoporosis, neuropathy, and vascular insufficiency compounded by increased Ca^{2+} requirements and weight gain during pregnancy. Pelvis osteodystrophy may be present as a result of CRF, dialysis, and prolonged steroid therapy, particularly if renal failure started in childhood. This may necessitate delivery by C/S due to cephalopelvic disproportion.

Maintaining normal glucose control may be challenging since the risk of developing gestational DM in the normal population is in the range of 0.15–12.30%.[33] In normal pregnancy, glucosuria is a common finding due to an increase in the filtered glucose load (increased GFR) and less efficient tubular reabsorption of glucose. Pregnancy outcomes in women with diabetic nephropathy may be better after a combined pancreas–kidney transplantation, than with a single kidney transplant.[33]

After total pancreatectomy and islet transplantation, parturients are not at increased risk for gestational DM or insulin dependency postpartum. Even segmental grafts appear able to produce enough insulin to overcome the peripheral insulin resistance found during the second and third trimesters.[34] Consequently, hyperglycemia may herald an ischemic insult, graft rejection, or a drug effect (steroids, CyA, tacrolimus).

Acute rejection and loss of a pancreas graft immediately after delivery has been reported.[33] With surgical placement of the pancreatic graft in the pelvis, the potential exists for compression-induced injury by the enlarging uterus or vaginal delivery. Graft pancreatitis caused by reflux of jejunal contents into the pancreatic duct should be suspected with the onset of abdominal pain and elevation of serum amylase and lipase levels. Confirmation requires ultrasound imaging of the uterus and kidney–pancreas grafts. The following mild-to-moderate complications have been reported: elevated amylase (that normalizes after delivery), preeclampsia, pancreatitis, hypertension, and urinary tract infection.

Liver recipients

The biochemical alterations in liver function found in normal pregnancy are summarized in Table 22.8.[35] All changes in LFTs are maximal in the third trimester except the decrease in albumin/total serum proteins and increase in fibrinogen occurring in the second trimester. Serum glutamic pyruvic transaminase (ALT or SGPT) and glutamic oxaloacetic transaminase (AST or SGOT) are considered the standard serological markers and most sensitive indicators of liver damage during pregnancy. During pregnancy, liver blood flow is essentially unchanged as the increase in blood volume and cardiac output (CO) is balanced by a decrease in the proportion of CO directed to the liver.[36] Alterations in drug distribution and metabolism are attributable to changes in protein binding, increases in plasma volume, extracellular water and adipose tissue mass, as well as a competitive inhibitory effect of estrogen on liver enzyme systems.

The incidence of hepatic dysfunction causing jaundice during normal pregnancy varies from 1:1500 to 1:5000, with viral hepatitis accounting for 50% of cases.[37] Derangements in liver and biliary function specific to pregnancy include: hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and rarely hepatic infarction or rupture, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and possibly acute cholelithiasis

Table 22.8 Biochemical alterations in liver function in normal pregnancy

Alkaline phosphatase	Increases up to 200% (placental > fetal bone isoenzymes)
Gamma glutamyl transpeptidase	Normal or increased, reduced response to hepatocellular injury
Aminotransferases (AST, ALT)	No change with slight increase, usually within the normal range, near term
Lactate dehydrogenase (LDH)	Increased
Bilirubin	Unchanged, or mild decrease or increase, rarely greater than 2 mg/dl
Total protein	Mild progressive decline
Alpha and beta globulins	Tend to increase
Gamma globulins	Tend to decrease
Albumin	Decrease 20–50%
Albumin-to-globulin ratio	Decreases
Triglyceride and cholesterol	Increase substantially (300% and 50%–100% respectively)
Ceruloplasmin	Gradually increased to term
Serum cholinesterase activity	Decreases by 30% at three days postpartum, rarely clinically significant prolongation of succinylcholine
PT and aPTT, bleeding time, platelet function	Unchanged
Fibrinolytic activity	Slightly reduced
Fibrinogen	Increases 50%, accounting for a hypercoagulable state
Factors VII, VIII, IX, and X	Increase
Platelet count	Decreases by 20% due to plasma volume expansion
Glucose	Fasting, decreased 10% or no change

PT = prothrombin time; aPTT = activated partial thromboplastin time

Table 22.9 Hallmarks of clinical rejection in the transplanted liver

1. Clinical signs	• Jaundice • Tenderness of the right upper quadrant of the abdomen • Asterixis
2. Biologic parameters	• Increased aminotransferases, alkaline phosphatase, bilirubin • Decreased serum albumin, coagulation factors
3. Liver biopsy	• Perivascular lipid accumulation • Periportal fibrosis • Cholestasis

(see Chapter 14). Hyperemesis gravidarum may result in a mild transient elevation in bilirubin and abnormal LFTs in up to 50% of patients, without chronic sequelae. In general, pregnancy does not appear to hasten the natural course of chronic liver disease, unless metabolic decompensation occurs early in the pregnancy.[35] Following liver transplantation, recurrence of the original disease is most frequently seen with hepatitis C. Recurrence of primary biliary cirrhosis and primary sclerosing cholangitis are still controversial. In patients with cirrhosis and portal hypertension, massive variceal bleeding in pregnancy is considered a significant risk, accounting for the majority of maternal deaths. In these patients, the incidence of premature delivery, placental insufficiency, and perinatal mortality is increased.

As limited information is available regarding the impact of pregnancy on graft function in the liver transplant patient, close surveillance of liver function with serial measurements of immunosuppressive drug levels is imperative. Graft rejection does not appear to be accelerated by pregnancy,[4,38,39] although mild to moderate increases in liver transaminases, progression of chronic rejection, and acute rejection episodes have been documented (see Table 22.9).[39] In the largest reported single center series, the incidence of elevated liver enzymes during pregnancy was 35%, with spontaneous resolution in greater than 80% of these patients without treatment.[40] The cause of persistently abnormal LFTs, unrelated to rejection, may be due to hepatotoxicity from azathioprine, CyA, and tacrolimus. Rejection may be successfully treated with steroid pulse therapy or adjustments in drug therapy, as it is common for drug levels to drop during pregnancy.

Obstetric and medical complications described in liver transplant recipients treated with CyA or tacrolimus and prednisone include renal insufficiency, preeclampsia, anemia, hyperbilirubinemia, and cytomegalovirus infection. The incidence of preeclampsia is 10–20%, and more frequent in women with preexisting renal dysfunction.[39]

End-stage liver disease is associated with unique systemic physiologic alterations (see Table 22.10). Liver transplantation does not fully correct the splanchnic and hyperdynamic systemic hemodynamic changes seen in advanced cirrhosis. Hepatic denervation after liver transplantation has no major deleterious effects on bile secretion, liver regeneration, or hepatic blood flow.[41] Total liver blood flow is increased, despite the

Table 22.10 Cardiovascular, pulmonary, and renal complications of advanced cirrhosis

Cardiovascular	"Hyperdynamic circulation" • High cardiac index and stroke volume • Low systemic vascular resistance • Low-to-normal mean arterial pressure (widened pulse pressure) • Mild tachycardia Central hypovolemia • Increased total blood volume • Decreased effective plasma volume • Increased sympathetic tone Hyporesponsiveness of the vasculature to pressor therapy Flow-dependent oxygen consumption Hepatic and splanchnic vasculature • Portal hypertension • Portal-systemic collateral circulation • Decreased hepatic blood flow
Pulmonary	Arterial hypoxemia (PaO_2 <70 mmHg) Intrapulmonary vascular abnormalities • Intrapulmonary shunting (precapillary or arteriovenous intrapulmonary vascular dilatations) • Portal-pulmonary or pleural shunting • Ventilation-perfusion mismatch (pleural effusions, ascites and diaphragm dysfunction, increased closing capacities, and/or aspiration pneumonitis) • Diffusion-perfusion defect (interstitial pneumonitis, fibrosis, or pulmonary hypertension) • Impaired hypoxic pulmonary vasoconstriction • Pulmonary hypertension • Hepatopulmonary syndrome Parenchymal abnormalities • Restrictive ventilatory pattern due to ascites limiting diaphragmatic excursion, pleural effusions, or chest wall deformity due to osteoporosis • Obstructive airway disease, emphysema, bronchitis-bronchiectasis • Interstitial lung disease (infection, pneumonitis, pulmonary edema)
Renal	• Renin-angiotensin-aldosterone activation: impaired sodium handling, water excretion, potassium metabolism, and concentrating ability • Impaired renal acidification • Prerenal insufficiency (ascites or diuretics) • Acute renal failure (acute liver failure, biliary obstruction, sepsis) • Hepatorenal syndrome • Glomerulopathies

return of portal pressures to normal, with persistence of portal-systemic collaterals evident four years after transplantation.[42] Portal venous inflow is still under the influence of normal vasomotor tone of the superior mesenteric artery, whereas the hepatic artery is denervated and this may account for the increase in hepatic perfusion. The potential long-term effect of persistently elevated liver blood flow on various metabolic pathways in the liver or disposition of high-hepatic-extraction drugs (e.g. lidocaine) is unknown.[43] Clinical implications of the loss of neural control of the hepatic vasculature may include an inability to vasoconstrict and shunt blood centrally in response to systemic hypotension, causing an increased susceptibility to hemorrhagic shock.[44] Postprandial hyperglycemia and insulin resistance, increased caloric intake due to a change in eating behavior, and reduced stimulation of hepatic progenitor cells in the canals of Hering are the major side effects of absent liver innervation. There is no evidence for hepatic sympathetic reinnervation within one year after liver transplant. However, there is evidence for regeneration of intrinsic nerves or regrowth of extrinsic nerves.[41]

Reported changes in systemic hemodynamics appear more controversial. Arterial hypertension and increased total systemic vascular resistance (SVR) are consistent findings, but the cardiac index can remain high in the presence of good liver function,[45] or it subsequently returns to a normal value.[42,44,46,47] Generally, the persistence of a high-output state is well tolerated. Significant increases in SVR due to a combined effect of the liver graft reversing the vasodilation in portal hypertension and to the inherent vasoconstrictor effect of CyA and tacrolimus, may be physiologically detrimental in patients with coexisting cardiomyopathy or left-sided valvular regurgitation. Myocardial ischemia may occur in patients with coronary spasm or accelerated arteriosclerotic disease secondary to CyA or tacrolimus and steroid therapy. The same hypercoagulable state contributing to hepatic artery thrombosis after liver transplantation may cause coronary thrombosis and myocardial ischemia postpartum, in the absence of significant coronary disease.[48]

Cytomegalovirus is the most common opportunistic viral infection in transplant recipients and, although frequently asymptomatic, may be associated with serious complications including pneumonitis, encephalitis, nephritis, hepatitis, and myocarditis.[49,50]

A liver transplant candidate may have pulmonary complications, such as infection (see Table 22.10). There is usually no evidence of the airway obstruction or bronchiolitis seen in bone marrow transplant recipients and heart–lung patients. Pulmonary hypertension in association with cirrhosis occurs in 1% of patients receiving liver transplants.[51] Moderate to severe pulmonary hypertension, especially with evidence of right ventricular (RV) dysfunction, increases the peripartum mortality rate. Resolution of pulmonary hypertension has been observed in survivors 13 months after liver transplantation.[52] Approximately 50% of all liver transplant candidates have some form of abnormal arterial oxygenation, frequently with a partial oxygen pressure <70 mmHg. Hepatopulmonary syndrome accounts for up to 50% of these patients, and is defined as the triad of hepatic dysfunction, pulmonary vascular dilatation, and abnormal arterial oxygenation (frequently $PaO_2 < 50$ mmHg).[53,54] A subset of patients with severe hypoxemia and intrapulmonary shunting showing response to 100% inspired oxygen and a type 1 angiographic vascular pattern, demonstrate normalization of arterial PaO_2 at rest and exercise from one to nine months following liver transplantation.[55,56,57]

Progressive severe osteoporosis and low back pain with vertebral fractures, related to osteodystrophy of chronic liver disease and the use of corticosteroids, is a frequent complaint in as many as 30–50% of patients. Recovery of bone mineral density may occur following transplantation.

Heart and heart–lung(s) recipients

In 1988, Lowenstein and colleagues reported the first successful pregnancy after cardiac transplantation.[58] However, information on the course and outcome of pregnancy in heart and heart–lung(s) transplant recipients is still very limited, with 86 cases reported up to the year 2002.[6,59,60,61,62,63,64,65,66] Large multicenter surveys have reported on 32 pregnancies in heart ($n = 29$) and heart–lung ($n = 3$) recipients resulting in 29 successful deliveries[67] and 47 pregnancies after heart transplantation in 35 women.[6] Published reports show that pregnancy in this patient population carries a high risk for maternal complications including: hypertension (48%), preeclampsia (24%), premature delivery, and worsening chronic renal insufficiency and preexisting hypertension.[68] Cholestatic jaundice has been described as a possible adverse effect of azathioprine.[69] Maternal infection is a concern, although it is relatively rare in practice.[70] The risk for these complications, however, is no higher than that reported in pregnancies after renal or liver transplantation. Good outcomes are expected unless there is coexisting morbidity or adverse effects from immunosuppressive drugs.

Patients considering pregnancy after cardiac transplantation should have normal cardiac function as determined by cardiac catheterization and echocardiographic studies and no evidence of rejection. Although acute rejection does not occur more often during pregnancy, the process of chronic rejection continues.[6,17,68,71] Histological examination of endomyocardial biopsies under fluoroscopy is considered the gold standard for surveillance of rejection in heart transplant patients.[72] A lead apron reduces exposure of the fetus to radiation during the biopsy in the first two trimesters.[73] However, a heavy lead apron applied to a supine woman during the third trimester may contribute to aortocaval compression.[74] Alternatives to fluoroscopically guided biopsies include the use of ultrasound guidance or assessment of functional status using noninvasive Doppler techniques. Most rejection is clinically silent and not associated with significant allograft dysfunction except in advanced cases.[75] Cardiac allograft rejection may correlate with electrocardiogram (EKG) findings of bradydysrhythmias, a decrease in voltage, ischemia or sustained ventricular tachycardia, ventricular fibrillation, and atrial flutter.[76] If the parturient discontinues immunosuppressive drugs against medical advice, she may present with the signs and symptoms of fulminant congestive heart failure: nausea, vomiting, cough, dyspnea, myalgias, arthralgias, fever, and hemodynamic instability. An echocardiogram will confirm the diagnosis showing a markedly increased

heart size and poor left ventricular function. Recognition of cardiac decompensation in the immunosuppressed patient may be clinically difficult as early fatigability, chest discomfort, dyspnea, orthopnea, palpitations, and peripheral edema may all occur during normal pregnancy and are related to changes in blood volume and hemodynamics.[77,78,79]

The normal cardiovascular response to pregnancy includes a rise in total blood volume, plasma volume, reduced SVR, and a 30% to 50% rise in CO, which peaks at 32 weeks' gestation. Cardiac output increases 15% during the latent phase of labor and 45% during the expulsive phase.[80] Postpartum there can be an 80% increase in CO due to autotransfusion from the uterus. The chronically denervated and nonrejecting heart has essentially normal ventricular contractile characteristics and cardiac reserve,[81] hence the cardiovascular changes of pregnancy should be well tolerated by the heart transplant patient.[82,83,84] The ejection fraction (EF) at rest is typically normal, with a low to normal CO and a heart rate (HR) of 95–115 beats/minute reflecting the intrinsic rate of depolarization at the donor sino-atrial node.[85] Although, functionally much improved, the maximal exercise capacity of cardiac recipients is typically reduced to 60–70% of predicted values compared with age matched sedentary normal controls.[86]

Denervated transplanted hearts lack the direct influence of autonomic neural control and must respond to the increased hemodynamic demands of pregnancy through adaptive intrinsic cardiac mechanisms. An increase in left ventricular end-diastolic volume mediates an increase in stroke volume and EF by means of the Frank-Starling mechanism, similar to that of a normal pregnant patient. This is followed by an increase in HR and contractility in response to circulating catecholamines.[75,87,88,89] As this HR response may take five or six minutes to manifest,[90] the patient may show exaggerated responses to hypovolemia, sudden changes in posture, or decreases in SVR. Denervation results in increased sensitivity to beta-adrenergic receptor blocking agents, exogenous catecholamine stimulation, and adenosine.[75] In the absence of changing cardiac function (e.g. acute rejection or development of accelerated coronary artery disease), intracardiac hemodynamics can be stable for at least six years posttransplantation.[91] However, a late, persistent, myocardial restrictive pattern has been identified that requires volume loading to characterize and it may reflect irreparable intrinsic myocardial damage.[92,93]

Although there is no histological evidence for afferent reinnervation of the cardiac allograft in humans,[94] functional reinnervation has been demonstrated by the reappearance of orthostatic cardiac acceleration, vasovagal reaction to head-up tilt, an increase in HR variability, and evidence of cardiac stores of norepinephrine.[95,96,97,98,99]

Late after cardiac transplantation the heart may have mildly elevated intracardiac pressures, functional tricuspid regurgitation with RV enlargement, unique "normal" physiologic alterations (see Table 22.11), and accelerated atherosclerosis (ACAD), all reflecting the effects of immunosuppressive therapy and the normal adaptive intrinsic mechanisms of the graft myocardium.[100] Angiographic evidence of ACAD is present in 10–20% of patients one year after transplantation and in up to 50% by five years,[101] the etiology of which is likely multifactorial.[102] The consequences of ACAD include myocardial infarction, congestive heart failure, and sudden death occurring at a rate of 1.9% per patient year after the first posttransplant year and accounting for more than one-third of late deaths.[103] The danger of ACAD lies in its frequently asymptomatic nature due to disruption of the afferent limb of the sympathetic nervous system that conveys the pain impulses of ischemia. However, angina pectoris occurs in as many as one-third of patients who present late after cardiac transplantation with proximal or mid-vessel coronary artery occlusion.[104]

Table 22.11 Pathophysiology of the transplanted heart: general considerations

1. Preload dependent with normal to mildly elevated filling pressures
2. Afterload: CyA-induced systemic hypertension, delayed or blunted blood pressure response
3. Sinus tachycardia, decrease in heart rate variability, delayed and attenuated heart rate response
4. Beta-adrenergic and cholinergic supersensitivity
5. EKG: "two P waves", some degree of right bundle-branch block in up to 70% of cases, increased incidence of atrial and ventricular dysrhythmias, sinus node dysfunction requiring permanent pacemaker insertion (implantation rates 4–29%), nonspecific ST segment abnormalities, and T wave inversion
6. Low-normal cardiac output, normal intrinsic contractility and reserve
7. Coronary circulation: autoregulation intact in the absence of rejection or coronary artery disease, accelerated atherosclerotic coronary artery disease, silent ischemia
8. Normalization of pulmonary artery pressure and pulmonary capillary wedge pressure

Patients with a pretransplant diagnosis of peripartum cardiomyopathy have not exhibited recurrence with subsequent pregnancies following cardiac transplantation. There is no evidence for atrial, pulmonary, or aortic suture line disruption from the generalized softening of collagen and the hemodynamic stresses of pregnancy.

Transplantation of the lungs en bloc results in loss of pulmonary innervation, bronchial arterial supply, and pulmonary lymphatic drainage. Loss of a cough reflex and inability to induce bronchoconstriction distal to the site of bronchial anastomosis, plus impaired lymphatic and mucociliary clearance mechanisms, will increase the risk of damage to the donor lung(s) from noxious stimuli or fluid overload. Reinnervation of the lungs[105] and re-establishment of lymphatic drainage has been demonstrated in the dog model,[106] but there is no good evidence of this in humans.

The hemodynamic indices of isolated cardiac and combined heart–lung transplant patients are strikingly similar.[93] At one-year follow-up, patients undergoing heart–lung transplantation have normal resting pulmonary arterial pressures (PAP), pulmonary vascular resistance (PVR), and CO, but elevated BP and SVR.[107] After single lung transplant for pulmonary hypertension, PVR and PAP decrease considerably and remain stable over a three-year

follow-up, with significant improvement in RV function.[108,109] In patients with end-stage pulmonary parenchymal disease, the donor lung is often perfused preferentially by virtue of its lower vascular resistance compared with the remaining diseased lung.[110]

The extent and time course of improvement in pulmonary function following transplantation is dependent on the disease treated and the use of single versus bilateral lung replacement.[111] Determinants of new lung function include a history of pulmonary edema at the time of implantation, postoperative infection, chronic rejection, and mechanical effects of tamponade from the native lung if obstructive airway disease is present.[112] The absence of pulmonary afferent nerves does not appear to be important for the control of respiration,[113] with return of forced expiratory volume (FEV1) and forced vital capacity (FVC) to near normal predicted preoperative values by six months in patients receiving bilateral lung replacement and single lung replacement for pulmonary hypertension.[111] The resting blood gases are usually normal, but there may be a compensated respiratory acidosis with hypercarbia.[112] Maximum oxygen consumption and indices of exercise capacity are significantly improved, but remain markedly below normal values.[111] In lung transplantation, obliterative bronchiolitis (OB) is the major factor limiting long-term survival. Bronchiolitis obliterans syndrome (BOS), defined as a staged decline in pulmonary function, has proved to be a reproducible and sensitive marker of obliterative bronchiolitis.[114] Bronchiolitis obliterans syndrome is the physiological surrogate for OB, which is now regarded as the end-result of numerous diverse insults in the allograft setting. The prevalence of OB in long-term survivors is between 20% and 50%, usually commencing from six months to two years following transplantation, and is characterized by airflow limitation in small airways manifested by decreasing FEV1.[111] There is a high incidence of BOS following lung transplantation, often associated with rapid progression and poor survival. It affects all modes of lung transplantation, regardless of sex, age, or underlying diagnosis. Acute rejection is a major prognostic factor. Lung infections after the onset of BOS worsen survival rates.[114] Progressive pulmonary failure from BOS and infection are the commonest causes of death in patients more than 100 days after transplantation.[115] As such, it has been suggested that women should postpone pregnancy until two years after transplantation. At this time their risk for developing OB can be assessed. Most physicians would caution against embarking on pregnancy if a woman developed BOS because of the likely adverse medium-term outcome (personal communication: Dr Paul Corris, Professor of Transplant Medicine, Newcastle-upon-Tyne, UK). Pregnancy posttransplant should be a carefully planned procedure with meticulous attention paid to BP and metabolic status.

Detecting rejection of a transplanted lung can be difficult, as signs and symptoms of fatigue, dyspnea, impairment of gas exchange, mild pyrexia, leukocytosis, and the development of infiltrates on chest x-ray may mimic those of infection.[110] The majority of acute rejection episodes occur in the first three months after transplant. The diagnosis is made using bronchoalveolar lavage and transbronchial lung biopsy. In heart–lung allografts, differential rejection may occur, and therefore one must monitor each organ independently.

The reader should refer to a comprehensive review of pregnancy and the lungs.[116] In a lung transplant patient with compromised lung function and limited respiratory reserve, the decrease in functional residual capacity, increased oxygen consumption at rest and during stress, and increased supine alveolar-arterial gradient seen during pregnancy make the patient more vulnerable to hypoxia.[117] Airway compromise from bronchomalacia and stenosis of the bronchial anastomosis may be exacerbated by mucosal engorgement, laryngeal edema associated with preeclampsia, volume overload, and upper respiratory tract infections.[118,119,120] Lung volumes and lung capacities are essentially unchanged by pregnancy, therefore a decrease in FEV1 by 10–20% may indicate significant pulmonary dysfunction.[111,115] A vital capacity (VC) of one liter had been suggested as the minimum functional requirement to maintain a successful pregnancy. There was little objective support for this particular value, and a successful pregnancy has been reported in a patient with a pretransplant VC of 800 ml.[121] In patients with residual pulmonary hypertension, elevations of CO and pulmonary blood volume, or a sudden increase in venous return from evacuation of the uterus and caval decompression may precipitate acute RV failure and cardiovascular collapse.

Obstetric experience in pregnancy after lung transplantation is limited.[122,123,124] In one report, three therapeutic abortions were performed, twice because excessive nausea and vomiting contributed to inadequate immunosuppressive drug levels and once because of allograft rejection.[122] In another report there were three successful pregnancy outcomes in lung transplant recipients with tacrolimus immunosuppression.[123] A third report described ten pregnancies in cystic fibrosis lung transplant recipients, which resulted in nine live births and one therapeutic abortion.[124] Five babies were premature but all nine children were well on long-term follow-up. However, four women died of chronic rejection within 38 months of delivery. The five mothers who survived had a long, stable interval between transplant and pregnancy (at least three years).[124] Female lung transplant recipients may have increased risks from pregnancy when compared to other solid organ recipients. As such, these pregnancies should be considered high risk and demand intensive obstetric and pulmonary monitoring.

Risks for the fetus and newborn

The state of health of the parturient, her genetic predisposition to transmit disease to the fetus, and immunosuppressive therapy all impact the physical status and developmental outcome of children born to mothers who have had an organ transplant. Compared with the general population, female transplant patients have a higher incidence of prematurity and low birthweight infants.[67] Prematurity (<37 weeks) is associated with an increase in neonatal complications compared with full-term births.[6] Numerous factors account for this finding including: drug therapy (immunosuppressive therapy or antihypertensive medications), persistent hypertension, renal insufficiency (serum creatinine >1.5 mg/dl), or vascular changes associated with an underlying systemic illness (DM). The spontaneous abortion rate is the same

Table 22.12 Commonly used immunosuppressive drugs in transplantation

	Animal reproductive data	Pregnancy category
Corticosteroids	Y	B
Azathioprine	Y	D
Cyclosporine A (CyA)	Y	C
Tacrolimus (FK506)	Y	C
Antithymocyte globulin (ATG)	N	C
Antithymocyte globulin (Thymoglobulin)	N	C
Orthoclone (OKT_3)	N	C
Mycophenolate mofetil (Cellcept)	Y	C
Basiliximab (Simulect)	Y	B
Daclizumab (Zenapax)	N	C
Sirolimus (Rapmune)	Y	C

as in the general population, estimated to be 15–20%.[64] Pregnancy following lung transplantation in the UK is associated with an increased risk of preeclampsia and small for gestational age (SGA) babies. However, neonatal growth is normal by six months (personal communication: Professor Corris).

Immunosuppressive drugs cross the placenta and, as such, may pose a risk to the fetus. Even with FDA categorization (B, no fetal risk; C, fetal risk cannot be ruled out; D, evidence of fetal risk), most of these drugs do not have established safety guidelines for use during pregnancy (see Table 22.12).[125]

The rate of congenital anomalies in neonates exposed to low therapeutic levels of immunosuppressive drugs in utero is the same as in the general population (3–5%). Overall, it appears that no pattern of fetal abnormalities has emerged with maternal corticosteroids, azathioprine, or CyA in either animal models or in human infants.[126] As such, these immunosuppressive agents are not considered to be teratogenic.[127] The long-term effects of immunosuppressive therapy on babies are unknown. In addition, concerns regarding the effect of maternal immune suppression on the germ cells of the offspring, and thus the next generation, have been raised. Based on transient impairment of T-, B- and NK-cell development and/or maturation, some authors suggest that continuous exposure to CyA in utero might alter the response of neonates to conventional vaccinations, which therefore might be delayed.[128]

Infectious disease complicating pregnancy in a transplant recipient can also affect the fetus and result in congenital defects. Cytomegalovirus infection (CMV) is a relatively common complication in transplant recipients. The majority of infants born with congenital CMV have no adverse sequelae. However, congenital CMV sepsis in the setting of primary maternal CMV infection, or rejection requiring increased immunosuppression, can cause fatalities in preterm infants. Exposure of the fetus to acyclovir during the first trimester of pregnancy is not associated with an increase in congenital abnormalities or rate of spontaneous abortion. Varying degrees of perceptual neurologic, psychomotor, or behavior complications have also been reported in infants with subclinical CMV infection. Spontaneous abortions, premature labor, and/or fetal demise may be associated with listeria monocytogenes, CMV, herpes-zoster, and rubella septicemia.[78,129] Whether there is an increased incidence of stillbirth is still being debated. The Toronto Renal Transplant Group followed 44 pregnancies of women who had received renal transplants.[130] There were 32 live-born children delivered by 26 mothers and 12 stillborn/abortuses, which is a statistically significant increase in the normal rate of stillbirth. Neonatal mortality was also higher than the 0.58% neonatal mortality rate in the general population of the US and supported by the European Dialysis and Transplant Association European Registry rate of 2.8% and the NTPR rate of 2%.[130]

Immunosuppressive drugs in pregnancy

Immunosuppressive protocols for pregnant allograft patients include various combinations of prednisone, azathioprine, CyA, and tacrolimus, with individual tailoring according to rejection episodes and side effects. The short-term effects of corticosteroids and azathioprine in pregnancy are well described from pregnancies in renal transplant recipients and in patients suffering from connective tissue disorders. Following the first successful pregnancy in a CyA-treated kidney recipient in 1983, and in a tacrolimus-treated liver transplant patient in 1993,[131,132] there had been limited information about the peripartum effects of these drugs. More recently, the NTPR has studied pregnancy outcomes in transplant recipients on CyA and nonCyA regimens.[19]

Although pregnancy is considered a state of immunologic tolerance, there is no evidence that episodes of rejection of any organ occur less frequently or that lower doses of immunosuppressants are necessary during pregnancy.[4] Therefore, drug therapy must be continued during pregnancy, with consideration given to the general recommendations listed in Table 22.13.

Prednisone

Prednisone is a synthetic 17-hydroxyglucocorticoid with potent anti-inflammatory activity introduced in 1963 for prophylactic immunosuppressive therapy against graft rejection. Maternal side effects include: hypertension, salt and water retention, obesity and cushingoid features, hyperglycemia, hyokalemia, skin fragility, nausea and vomiting, gastric ulceration and hemorrhage, myopathy, “steroid psychosis,” pancreatitis, increased susceptibility to infection, and poor wound healing.[133] Osteoporosis with compression fractures and aseptic necrosis of the hip, knee, shoulder, and elbow with proximal muscle weakness necessitates careful positioning. The psychological effects of prednisone range from slight mood changes to fulminant psychosis. These patients may be at increased risk for postpartum depression. Hypercholesterolemia is one possible mechanism contributing to corticosteroid-induced vascular damage and an increased incidence of accelerated coronary atherosclerosis seen in heart and renal transplant patients.[134]

Table 22.13 Recommendations for immunosuppressive therapy during pregnancy

1. Maintain immunosuppressive therapy at prepregnancy levels unless signs of toxicity or acute rejection mandate changes
2. Monitor patient for adverse effects attributable to specific drugs
3. Consider all patients susceptible to life-threatening infections; aseptic technique and the administration of prophylactic antibiotics prior to any invasive procedure is necessary
4. Breast-feeding should be discouraged in patients taking CyA, tacrolimus, and/or azathioprine due to the transfer of these drugs to breast milk, and the uncertainty of drug exposure in the newborn
5. Steroid supplementation is required for the stress of labor and delivery
6. Adjustments in the dose of azathioprine may be indicated if there is evidence of acute rejection, a decrease in maternal leukocyte or platelet counts, or abnormal liver function tests
7. Close monitoring of CyA doses is crucial; there are considerable discrepancies regarding requirements, especially in the third trimester and the immediate postdelivery period
8. Patient noncompliance with medications must be detected early or may result in severe deterioration or loss of graft function

Reports of IUGR and low birthweight neonates are common for azathioprine and CyA regimens (containing prednisone), with the individual contributory effect of each drug undetermined.[135,136] Complications in infants born to mothers on steroid therapy include thymic hypoplasia, depressed hematopoiesis, lymphocytopenia, and rarely adrenal insufficiency. These problems are unlikely if a woman's prednisone dose has been decreased to 15 mg/d.[16] Doses of prednisone greater than 20 mg/d have been associated with serious maternal infection. Prednisone readily crosses the placenta; however, the fetus is unable to convert prednisone to prednisolone, which accounts for fetal levels only 10% of those seen in the mother. Maternal doses of <15 mg/day are insufficient to accelerate fetal lung maturation, with the subsequent risk of respiratory distress syndrome in the premature infant. A high incidence of preterm delivery associated with premature rupture of membranes has been attributed to long-term steroid therapy.[26] Weakening of connective tissue may also predispose to uterine rupture.

Steroid therapy is continued during pregnancy at prepregnancy dosing, with high-dose therapy indicated for treatment of episodes of acute rejection. Augmenting steroids postpartum to cover "rebound immunoresponsiveness" is a controversial issue.[17,137] With little evidence of beneficial effect, the current practice is to continue baseline therapy postpartum. It is uncertain whether a history of exogenous steroid administration, followed by surgical stress with no supplementation, precipitates acute adrenal insufficiency.[138] In reality, few patients with suppressed adrenal function and no steroid supplement develop hypotension following surgery. The diagnosis of adrenal insufficiency is primarily one of exclusion. However, supplemental high-dose steroid therapy has little associated morbidity and should be administered during labor and delivery to cover maximum stress requirements equivalent to cortisol 200–500 mg/day. An adrenal crisis is life threatening and should be anticipated based on changes to vital signs, temperature, serum glucose, and electrolytes. However, many of the symptoms of adrenal crisis can be masked by similar symptoms that are possible during normal labor, namely nausea and vomiting, abdominal pain, back pain, dizziness, syncope, low grade fever, headache, and lethargy.

A reduction of plasma cholinesterase activity by 50% in patients on long-term prednisone therapy[139] may prolong the duration of action of succinylcholine. Antagonism of pancuronium-induced blockade by interaction between the steroid-based pancuronium nucleus and corticosteroids, or modulation of choline uptake presynaptically, have been reported.[140,141,142]

Cyclosporine

Cyclosporine is a major anticalcineurin agent and the drug of choice for chronic maintenance immunosuppression, and for treatment of acute rejection in solid-organ transplantation. Cyclosporine A is an 11-amino acid cyclic polypeptide molecule extracted from soil fungus that inhibits lymphokine production and release (macrophage IL-1 and helper T lymphocyte IL-2) and selectively inhibits helper and cytotoxic T cells by blocking antigen-induced T-cell activation, without bone marrow suppression (see Figure 22.1).[143,144] A "safe fetal dose" for CyA has not been established. Prepregnancy therapeutic levels should be maintained, keeping the daily dose low, preferably at 2 to 4 mg/kg/day for renal transplant patients. Blood concentrations of CyA are measured regularly, with the aim of maintaining a therapeutic trough concentration of 100 to 300 ng/l. Monitoring drug concentrations is essential as underdosing may precipitate graft rejection. The risks from excessive immunosuppression include systemic toxicity, increased neoplastic and infection risks, and altered graft function. Formulations of CyA include Sandimmun® and Neoral® soft gelatin capsules and oral solution, and a concentrate for intravenous (i.v.) infusion. Potential risks of its use include lipid-necrosis of the lung with aspiration of the oral forms, and hypersensitivity reactions. Intravenous CyA contains the solvent Cremophor EL® (polyoxethylated castor oil), which together have been linked to anaphylactoid reactions (incidence <1:1000 cases), histamine release, nephrotoxicity, cholestasis, and an interaction with nondepolarizing muscle relaxants.[145,146,147] Central venous administration of CyA may result in hyperkalemia, coronary vasoconstriction, and adult respiratory distress syndrome.[148,149] Limiting i.v. infusion rates to 2 mg/kg over a period of one hour is recommended.[148]

Both increases and decreases in cyclosporine blood levels can occur during pregnancy.[150] Cyclosporine A requirements may increase during pregnancy, from decreased bioavailability, altered tissue distribution, and increased metabolism.[10,151,152,153] The volume of distribution may be increased, but because of increased red cell mass, a greater portion of any given dose is red cell bound.[154] This effect may be offset by increased circulating sex steroids, which inhibit liver microsomes (cytochrome

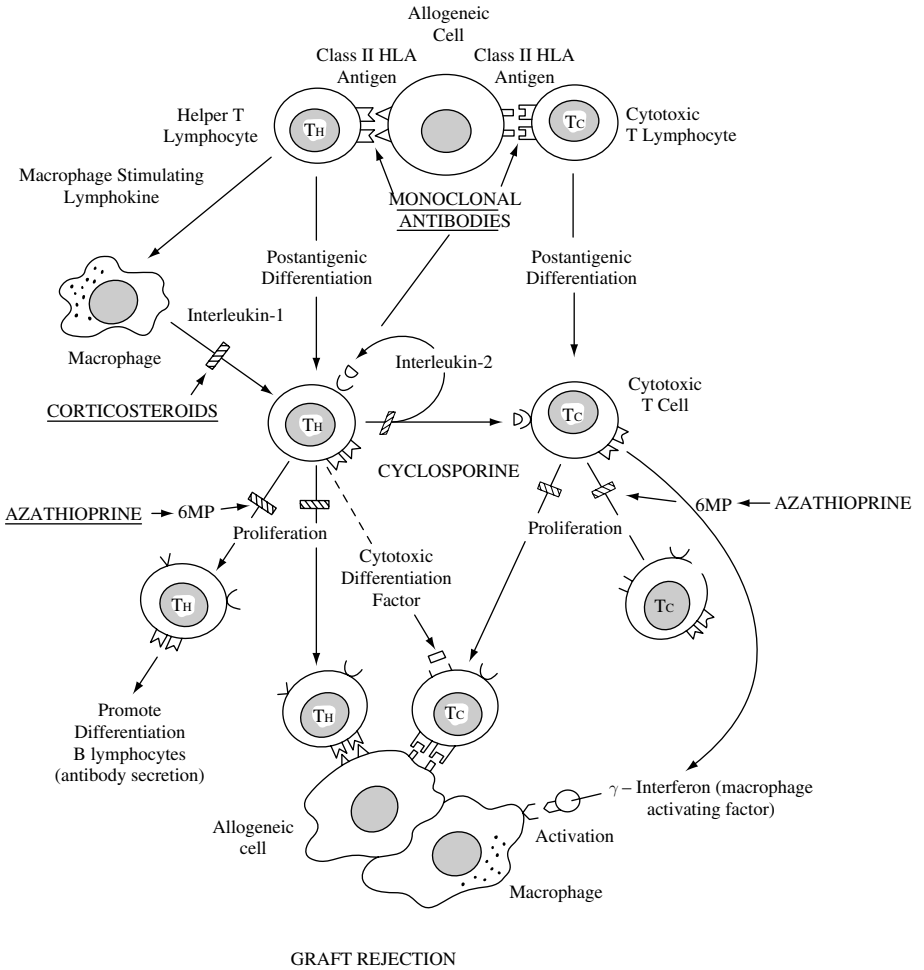

Figure 22.1 Schematic representation of graft rejection and the sites of action of the currently used immunosuppressive agents: azathoprine, corticosteroids, cyclosporine, and monoclonal antibodies. (From Flye, M. W. Immunosuppressive therapy. In Flye, M. W. (ed.) *Principles of Organ Transplantation*. Philadelphia: W. B. Saunders, 1989, pp. 155–75.)

P-450 IIIA) and impair hepatic clearance of CyA.[153] Interpatient variability in CyA pharmacokinetics following oral administration, may account for reports of no appreciable change in dosing schedules.[155] Possible effects of the normal physiological changes of pregnancy on drug distribution, metabolism, and clearance have been summarized elsewhere.

Cyclosporine A readily crosses the placenta with fetal levels ranging anywhere from 10% to 50% of maternal levels.[151] Fetal side effects are dose dependent and include an increased incidence of IUGR, prematurity, and low birthweight. The NTPR noted a low birthweight (<2500 g) in 49.5% and a very low birthweight in (<1500 g) 17.8% of 107 infants born to transplant recipients taking cyclosporine during pregnancy.[19] Intrauterine growth restriction may be associated with a reduction in nephron number and oligomeganephronia. Therefore offspring of organ transplant women treated with CyA may have a theoretical risk of renal impairment, due to IUGR and fetal nephrotoxicity.[156] Overall, the pregnancy success rate with CyA appears comparable to that with azathioprine.[7,19] There is evidence that CyA has adverse effects on endothelial cell function, lipoprotein metabolism, placental prostanoid production, and platelet function. A combination of these factors, and longstanding hypertension, may contribute to placental insufficiency and account for a 30% incidence of preeclampsia.[157,158] Cyclosporine is excreted in human breast milk and breast-feeding is contraindicated due to the potential for immune suppression, renal toxicity, an effect on growth, and possible carcinogenesis.[159] However, given that the concentration of CyA in breast milk is usually <10% of therapeutic blood levels, and that breast-fed infants have shown undetectable blood CyA levels, in the absence of detectable adverse effects women taking CyA have been allowed to breast-feed their infants. Blood CyA levels must be monitored in the infant to ensure that the level of exposure is less than 5% to 10% of the therapeutic dose.[154,160,161]

Nephrotoxicity and hypertension complicate CyA therapy in virtually every patient. Cyclosporine-treated mothers are more likely to be hypertensive before pregnancy (51.7%) as compared with mothers treated with other regimens (18.5%). Three etiologic mechanisms have been postulated including: increased proximal renal tubular pressure, decreased filtration coefficient, and vasoconstriction.[162,163] Nephrotoxicity is manifested as a dose-dependent decrease in maternal GFR, with decreased creatinine clearance, increased blood urea nitrogen and creatinine, hyperkalemia, hyperuricemia, hypertension, and hyperkalemic hyperchloremic renal tubular acidosis. Renal function, fluid balance, and electrolyte levels should be monitored

closely. Concomitant administration of drugs known to have nephrotoxic potential and those dependent on renal elimination should be avoided.

Additional complications of CyA include: mild hepatic dysfunction, pancreatobiliary complications, hypochromic anemia, fatigue, hypertrichosis, gum hyperplasia, predisposition to thromboembolic phenomena, and rarely a hemolytic-uremic-like syndrome. Glucose intolerance and hyperinsulinemia, which may progress to overt DM, is associated with an increased risk of atherosclerosis – a leading cause of death in long-term survivors of solid organ transplants.[164,165,166]

Various neurologic sequelae have been reported in 20 to 50% of patients treated with CyA including tremor, seizures, cerebellar dysfunction, encephalopathy, neuropathy, and motor deficit syndromes.[167,168] Paresthesia of the distal extremities (especially hands) is more common than focal weakness, although evidence of combined demyelination and axonal damage has been reported.[169] Most neurotoxic side effects of CyA are completely reversible with drug withdrawal.[167]

When considering regional anesthesia, document any existing neurologic deficit and avoid hypomagnesemia, which can potentiate CyA-induced neurotoxicity. Also, exercise care with patient positioning. Another concern is concurrent viral or opportunistic central nervous system (CNS) infection, frequently presenting with few clinical findings and reported in approximately 5–10% of transplant patients. Neurological complications of organ transplantation may also result from progression of the underlying disease process, a complication of the surgical procedure, or as a unique feature of a specific transplant type.[167]

The possibility exists of interactions between CyA and any drug acting as a substrate for cytochrome P-450.[170,171,172] A potential for drug interactions with CyA has been described for macrolide antibiotics, azole antifungal drugs, Ca^{2+} channel blockers (excluding nifedipine), histamine H2-receptor antagonists, nonsteroidal antiinflammatory agents, and any nephrotoxic drug. Agents commonly used in anesthetic practice that demonstrate modified pharmacodynamic action include benzodiazepines, neuromuscular blocking agents, opioids, antibiotics, and propofol. Isoflurane decreases the rate of absorption of CyA by reducing gastric emptying and absorption from the proximal small bowel.[173] Oral doses should be given 4–7 hours preoperatively, as the formulation contains olive oil, castor oil, or corn oil, and represents a significant risk if regurgitation and aspiration should occur. In addition, the desired therapeutic blood levels may not be achieved if given outside of this time interval. Cyclosporine has been shown to prolong nondepolarizing neuromuscular blockade,[145,146,174,175,176,177] from a combined effect of the parent drug, causing inhibition of Ca^{2+} entry into the muscle cell, and Cremophor®, which interferes with drug binding. This increases the concentration of nondepolarizing drugs at the neuromuscular junction. Cyclosporine A has been reported to improve analgesia from fentanyl in a dose-dependent manner and to increase pentobarbital hypnosis.[178] The clinical significance of this data is uncertain.

The potential for CyA and anesthetic agents to interact is important, because many anesthetics cause liver enzyme induction, which can alter CyA levels seven to ten days later and potentiate CyA-related side effects.

Azathioprine

Azathioprine in combination with prednisone was conventional immunosuppressive therapy in transplant recipients from 1961 until the introduction of CyA in 1978. The normal maintenance dose is 1–2 mg/kg, with a reduction required if bone marrow depression or liver toxicity occurs. Additional maternal effects include: rashes, gastrointestinal manifestations, pancreatitis, and increased risk of neoplasm and infection. Reversible interstitial pneumonitis has been reported as a hypersensitivity reaction.[179] Azathioprine crosses the placenta, achieving fetal blood concentrations that are 63% to 93% of those in maternal blood.[180] Theoretically, the fetus should be protected from the effects of azathioprine during the period of organogenesis as the fetal liver lacks the enzyme inosinate pyrophosphorylase, required for conversion of the parent drug to its active metabolites. Fetal and neonatal effects include: bone marrow toxicity, IUGR, sepsis, transient lymphocyte chromosomal damage and concerns of developing malignancies, congenital anomalies, and infertility in the next generation. Azathioprine may be associated with SGA babies. Mice exposed to 3 mg/kg of 6-mercaptopurine in utero had lower rates of conception and increased fetal loss as adults (46%).[181]

Human and animal studies show that azathioprine potentiates succinylcholine-induced muscle relaxation[182] and antagonizes nondepolarizing neuromuscular blockade by presynaptic inhibition of the motor nerve terminal.[182,183,184]

Tacrolimus

Tacrolimus (Prograf®, FK506) is the newest macrolide immunosuppressive agent introduced into clinical trials in April 1990. It functions by inhibiting the synthesis of IL-2 and other lymphokines and causing T-cell activation and proliferation.[185,186] The pharmacokinetic profile is similar to CyA with P-450 liver enzyme metabolism, but tacrolimus does not require bile acids for solubilization and absorption. Advantages over CyA include greater potency, a hepatotrophic effect, increased steroid-sparing and less hypertension, hypercholesterolemia, hyperuricemia, or serious infections. The incidence of new-onset DM, nephrotoxicity, and gastrointestinal tract complaints with tacrolimus is similar to that of CyA.[187] Neurologic complications include seizures, central pontine myelinolysis with dysarthria, and motor disturbances, which resolve with dose reduction.[188] Headache and insomnia are other common dose-related complaints. Animals immunosuppressed with tacrolimus, when compared with CyA, develop more significant coronary artery disease over just four weeks in the transplanted and native heart.[189]

Tacrolimus crosses the placenta, and umbilical cord concentrations are approximately 50% of maternal concentrations. Transient unexplained hyperkalemia, which resolves spontaneously within 24 to 48 hours, has been reported in the newborn of liver transplant recipients taking tacrolimus during pregnancy.[131] As with other immunosuppressive agents, therapeutic dosing of tacrolimus has

demonstrated no teratogenic activity in humans. In a limited number of published reports, birthweights are normal for gestational age, which may be a result of steroid withdrawal or it may represent an intrinsic property of tacrolimus.[131,132]

Mycophenolate mofetil

Mycophenolate mofetil use for immunosuppression after renal transplantation has increased from 11.9% in 1995 to 79.6% in 2002.[190] Mycophenolate mofetil is rapidly absorbed after oral administration and is hydrolyzed to mycophenolic acid. Mycophenolic acid is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase, blocking de novo purine biosynthesis, essential for lymphocyte proliferation. In 2002, the NTPR reported poor fetal outcomes after mycophenolate mofetil exposure during pregnancy.[125] Due to the long half-life of the drug, proven teratogenic potential in animals, and lack of human data, current recommendations are to withdraw mycophenolate mofetil six weeks before conception in transplant recipients planning a pregnancy.[191,192,193]

Sirolimus

Sirolimus (rapamycin or Rapamune®) is a relatively new immunosuppressant and antiproliferative drug used to prevent rejection in kidney transplant recipients. Sirolimus is a macrolide antibiotic (*"-mycin"*) by-product of the bacterium *Streptomyces hygroscopicus*, which inhibits the response to IL-2 and thereby blocks activation of T- and B-cells. The chief advantage of sirolimus over calcineurin inhibitors, like cyclosporine and tacrolimus, is that it is not toxic to kidneys. Sirolimus can be used alone or in conjunction with calcineurin inhibitors and/or mycophenolate mofetil, to provide steroid-free immunosuppression regimes. Its optimal role in immunosuppression has not yet been determined and is the subject of a number of ongoing clinical trials.[194]

Monoclonal and polyclonal antibodies

Orthoclone OKT3® is an anti-CD3 monoclonal antibody that can cross the placenta. The NTPR has reported treatment of five women with OKT3 during pregnancy with four surviving infants.[19] The effect of polyclonal antibodies on the developing fetus is unknown but the immunoglobin component would be expected to cross the placenta.

Anesthetic considerations for labor and delivery

General considerations

Collaboration of a multidisciplinary team is essential in the antenatal assessment and peripartum management of the transplant recipient. Preferably, the patient should be seen in consultation by an attending anesthesiologist early in the third trimester, as preterm labor and delivery is common. The evaluation should consist of a thorough history and physical examination, and review of the patient's medical records and personal diary with special attention given to assessment of maternal antenatal problems, immunosuppressive therapy, graft function, and fetal surveillance (see Table 22.14). Spontaneous onset of labor with vaginal delivery is the ultimate goal, with C/S reserved for obstetric indications only. In patients in whom the transplanted kidney or pancreatic graft is placed in the pelvis close to the uterus, there is no evidence to substantiate the fear of organ injury during vaginal delivery or dysfunction from compression by the enlarging uterus. Dystocia is a rare complication.[195] The patient should be encouraged to deliver in a hospital-based setting that is equipped with a high-risk maternal and fetal monitoring unit and an intensive care facility.

Table 22.14 Antenatal assessment of the transplant recipient

1. Maternal problems
   - Pregnancy
     - Renal dysfunction: monthly urine cultures, treating asymptomatic infections, monitoring BP, proteinuria, and weight every 2–4 weeks
     - Hypertension/preeclampsia: change hypotensive drugs to those tolerated during pregnancy, abolishing ACE-inhibitors and angiotensin II receptor antagonists
     - Monitoring of most common viral infections: titers of anti CMV IgG and IgM every three months; test for toxoplasmosis every six months; cervical culture for herpes infection before delivery
     - Screen for gestational diabetes
   - Coexisting systemic disease process
   - Transplant surgery-related
2. Immunosuppressive therapy
   - Monitor drug levels, modifying dosages according to pharmacokinetic changes during pregnancy
   - Complications, toxicities, adverse reactions
   - Drug interactions
3. Graft function
   - Detection of acute/chronic rejection, ischemia, or failure
   - Physiologic adaptations to pregnancy
   - Laboratory and diagnostic studies
4. Fetal surveillance
5. Monitoring pregnancy by obstetrician and transplant physicians as a high-risk pregnancy

Tocolytic therapy for managing preterm labor includes magnesium, nifedipine, and beta agonists (terbutaline and ritodrine). These medications are probably safe for use in renal and liver transplant recipients.[196] There are no case reports discussing the use of beta-agonists in the cardiac transplant recipient, but they probably should not be used in this population.[196] Indomethacin should be avoided as it may potentiate cyclosporine nephrotoxicity.[197] It is vital to maintain a good urine output perioperatively, as any further renal insults from drugs or periods of low CO may be additive and can cause rapid development of anuria.[198]

Aseptic technique is essential: handling all intravascular and airway equipment with sterile gloves and using prophylactic

antibiotics is essential to protect the patient from nosocomial infections. Invasive procedures such as fetal monitoring with a scalp electrode, intrauterine pressure monitoring, placement of a urinary bladder catheter, or central venous and arterial cannulation carry an increased theoretical risk of infection in transplant recipients. However, there are no reports in the literature suggesting an increased risk of these infectious complications in the immunosuppressed pregnant patient,[89] so one must weigh the risk to benefit ratio. Endotracheal intubation via the orotracheal route is preferable given the possibility of technical difficulty from nasal mucosal edema, risk of epistaxis, and the potential for infection by diphtheroids and staphylococcal commensals from the nasopharynx and skin.

Transfusion practices should take into consideration the Rhesus titer and CMV status of the patient. Institutional practices vary from administering only CMV-negative blood products to all transplanted patients or exclusively to the CMV-negative recipient who has received a CMV-negative organ; white-cell filtering the blood and platelets to prevent transmission of CMV carried in the leukocytes; and/or irradiation to destroy T cells, which provoke graft versus host disease.

Virtually all anesthetic techniques have been used successfully in transplant recipients for labor analgesia and forceps-assisted or surgical delivery. The anesthetic technique will depend on (1) obstetrical considerations; (2) evidence of graft dysfunction; (3) the use of drugs and techniques to minimize additional insult or physiological trespass to the transplanted organ; (4) the presence of absolute or relative contraindications to regional anesthesia; and (5) individual preferences. Continuation of aspirin, azathioprine, and dipyridamole in the peripartum period could theoretically affect platelet adhesiveness, but in the absence of overt platelet dysfunction most clinicians would not consider these a contraindication to the use of regional anesthesia. Routine immunosuppressive therapy should be continued, while monitoring for signs of toxicity. The anesthetic problems associated with long-term steroid, azathioprine, CyA, or tacrolimus therapies are summarized in Table 22.15.

Kidney and pancreas–kidney

Coexisting systemic disease and residual physiologic alterations of end-stage renal disease may have a pronounced impact on anesthetic management in this group of women (see Table 22.7). In addition, patients should be monitored appropriately (see Table 22.5) and graft function optimized (see Table 22.16). Ischemic renal injury and potential nephrotoxins should be avoided. Deterioration of renal function may necessitate the use of hemodialysis, with its inherent complications. Patients with a history of CRF have a high incidence of viral hepatitis (types B, C, and HIV). This may result in hepatic dysfunction in the recipient. There is a potential for significant accumulation and prolongation of the effect of anesthetic agents dependent on renal metabolism and elimination. Caution should be exercised in the use of succinylcholine for intubation in a patient with peripheral neuropathy or hyperkalemia resulting from renal insufficiency, or CyA and terbutaline administration. Cisatracurium is a good alternate choice, as there are no adverse neonatal effects at this intubating dose. Correct hypercalcemia, if possible, prior to administration of anesthesia with monitoring of ionized serum Ca^{2+}, potassium, and magnesium, volume status, renal and cardiac function, and avoid metabolic or respiratory acidosis, which raises the ionized Ca^{2+} concentration even further. Responses to anesthetic agents are not predictable.

Liver

Specific peri-anesthetic considerations for patients with liver disease and the pregnant patient with significant hepatic dysfunction are reviewed in detail elsewhere (see Chapter 14).

In the liver transplant patient, analgesia for labor and delivery or anesthesia for C/S can be administered as in the healthy parturient if liver function is stable and coagulation is within normal limits. The "healthy" transplanted liver is no more susceptible to potentially hepatotoxic drugs (e.g. halothane) than the liver of a normal patient.[199]

Continuing evidence of portal hypertension, and the possibility of large venous collaterals, is a relative contraindication for placement of an epidural catheter, with increased risk of vessel penetration and possible hematoma formation.[199] Mild to severe graft dysfunction from acute or chronic rejection, recurrence of hepatitis, or malignancy, may lead to altered drug distribution, coagulopathy, and portal hypertension. This has implications for provision of regional anesthesia, variceal bleeding with Valsalva maneuvers or insertion of a nasogastric tube, decreased anesthetic requirements, maintenance of hepatic blood flow, and avoidance of potential hepatotoxins.

The disposition and pharmacological effects of drugs in patients with chronic liver disease and the ability of the newly transplanted liver to metabolize and eliminate drugs are poorly described. Caution should be exercised in the administration of all agents, as the pharmacokinetic and pharmacodynamic properties of each drug depend on a composite of different factors including: altered graft function (rejection, recurrence of the primary disease process, nonspecific hepatocellular damage, or cholestasis), persistent pathophysiologic changes characteristic of end-stage liver disease, and drug interactions or toxic effects of the immunosuppressive therapy. Possible effects of the normal physiological changes of pregnancy on drug distribution, metabolism, and clearance have been summarized elsewhere.[200]

Hepatic extraction of morphine, fentanyl, and vecuronium is well handled by the newly transplanted liver.[201] In one study, morphine use following liver transplantation was significantly reduced for 72 hours compared to patients following liver resection.[202] There were no differences in pain or sedation scores. Factors that most likely account for this difference include altered pain perception (steroids, cerebrospinal fluid endorphins, low grade encephalopathy, liver denervation, CyA, personality traits), or persistent pharmacokinetic and pharmacodynamic changes inherent in end-stage liver disease. It has yet to be determined whether this significant difference persists long term.[202] Accumulation of active morphine metabolites with prolonged narcosis should be anticipated in patients with impaired renal function.[203]

Table 22.15 Complications and anesthetic considerations of immunosuppressive therapy

Cyclosporine	• Neurologic sequelae (tremor, seizures, cerebellar dysfunction, encephalopathy, neuropathy, motor deficit syndromes, fatigue) • ARDS • Aspiration pneumonitis • Hypertension, vasoconstriction • Accelerated atherosclerosis, hypercholesterolemia • Nephrotoxicity and enhanced susceptibility to renal insults • Hyperkalemic hyperchloremic renal tubular acidosis • Hemolytic-uremic-like syndrome • Glucose intolerance • Hyperkalemia, hypomagnesemia • Hepatic dysfunction and pancreatobiliary complications • Hypertrichosis, gum hyperplasia • Predisposition to thromboembolic phenomena • Increased neoplastic and infection risk • Hypersensitivity reactions, histamine release • Drug interactions: (P-450 III A microsomal enzymes) • Prolongs nondepolarizing neuromuscular blockade • Increases fentanyl analgesia
Tacrolimus	• Neurologic sequelae (seizures, central pontine myelinolysis, headache, insomnia) • Hypertension, accelerated atherosclerosis, hypercholesterolemia • Glucose intolerance • Nephrotoxicity • Gastrointestinal tract complaints, hepatotrophic effect • Infection and neoplastic risk • Hyperkalemia
Azathioprine	• Bone marrow depression (lymphopenia, thrombocytopenia, anemia) and synergy with other marrow suppressants • Hepatic dysfunction and jaundice • Hypersensitivity reactions, rashes • Gastrointestinal manifestations, pancreatitis • Infection and neoplastic risk • Drug interactions: potentiation of depolarizing and antagonism of nondepolarizing neuromuscular blockade
Prednisone	• Psychological effects (mood changes to psychosis) • Hypertension, salt and water retention, accelerated atherosclerosis • Obesity and cushingoid features • Adrenal insufficiency • Hyperglycemia, hypokalemia • Osteoporosis, compression fractures, aseptic necrosis, skin fragility, short stature • Proximal myopathy • Peptic ulcer disease, nausea and vomiting, pancreatitis • Poor wound healing • Increased susceptibility to infection • Drug interactions: reduction of plasma cholinesterase activity • Antagonism of pancuronium effects

Table 22.16 Achieving optimum function of the transplanted kidney

1. Maintain a homeostatic environment (fluids, electrolytes, acid-base status, hematocrit)
2. Cardiovascular stability (systolic blood pressure 120–140 mmHg)
3. Intravascular volume expansion to a CVP 12–15 mmHg
4. Drug therapy: dopamine 2.5–5 μg/kg/min, mannitol 25 g i.v., lasix 40–400 mg i.v.
5. Avoid nephrotoxic agents
6. Anticipate alterations in drug pharmacokinetics and pharmacodynamics
7. Recognize and treat rejection, infection, or acute tubular necrosis

Clinically, the pharmacokinetics of a prolonged infusion of propofol for 48 hours following liver transplantation are identical to those in patients with no evidence of hepatic disease.[204] In contrast, the human cytochrome P-450 monooxygenase system is suppressed by propofol in vitro, which suggests that potential drug interactions may exist between propofol and substrates, such as CyA, which use cytochrome P-450 for drug metabolism.[205]

As bupivacaine is eliminated almost entirely by hepatic metabolism, impairment of hepatic function in conjunction with repeated drug doses could result in drug accumulation, with the risk of central nervous system (CNS) and cardiovascular toxicity. Repeated bilateral intercostal injections of bupivacaine have been used immediately following liver transplantation to provide analgesia, limiting the need for the systemic administration of opioids. Pharmacokinetic studies reveal prolonged elimination of both enantiomers of bupivacaine with no tendency for accumulation, even upon repeated dosing.[206]

During the reperfusion phase of liver transplantation, there is progressive recovery of cytochrome P-450-dependent microsomal enzyme activity starting immediately after unclamping the portal vein and inferior vena cava.[207] Therefore, neuromuscular blocking agents that are eliminated by the liver (e.g. vecuronium, rocuronium, pipecuronium) are suitable for use in patients with normal liver graft function.[207,208] Plasma concentrations and the neuromuscular effect of atracurium are not influenced by the absence of hepatic function or circulation, although an accumulation of its metabolite, laudanosine, has been reported.[207,209]

In all liver transplant patients, large-bore i.v. access is essential for the rapid administration of fluids and blood products, as required. The patient may be at risk for intraoperative hemorrhage from excessive surgical blood loss due to the presence of

residual portal-systemic collaterals, a mild to moderate coagulopathy, and the clinical impression of a decreased capacity of the denervated hepatic vasculature to compensate for systemic hypotension.

Heart and heart–lung(s)

In the heart or heart–lung(s) transplant patient, invasive hemodynamic monitoring may be useful to assess the balance between peripheral vasodilatation and volume loading. Indications include: a suspicion of cardiac decompensation during an acute rejection episode; preexisting marginal cardiac reserve from chronic rejection; myocardial ischemia; or if large fluid volume shifts are anticipated. Additional indications include oliguria unresponsive to fluids; respiratory compromise; and the need for short-acting vasoactive medications (e.g. sodium nitroprusside).[196] In most instances, a minimum amount of monitoring is needed for these patients.[210] The left internal jugular, antecubital, or subclavian veins are preferred for central venous cannulation to keep the right side of the neck available for rejection surveillance using serial endomyocardial biopsies of the right ventricle.[198] Radial artery lines are preferable to femoral artery lines, wherever possible.[112] Transesophageal echocardiography may provide the least invasive method to evaluate ventricular filling and contractility. Infective endocarditis is a rare complication;[211] however, routine administration of standard endocarditis prophylaxis according to the American Heart Association guidelines is recommended on the basis of the immunocompromised condition of the patients and the theoretical risk of suture-line infection.[75]

In the absence of reflex vasoconstriction following hypovolemia, these patients are exquisitely sensitive to changes in preload and as such require attention to left-sided uterine displacement and volume loading. Before instituting spinal or epidural anesthesia for C/S, preloading the "compromised" patient with a colloid solution is felt by some authors to be more efficacious than a crystalloid preload in preventing hypotension.[196] Cautious titration of drugs is imperative, with the avoidance or judicious use of myocardial depressants. The anesthetized patient with a heart transplant may show exaggerated responses to hypovolemia, orthostatic hypotension, or decreases in SVR.[110] Treatment of hypotension includes adequate volume loading and the availability of an infusion of isoproterenol, epinephrine, or dobutamine to increase the HR rapidly and improve cardiac contractility. Most reports indicate that despite both direct and indirect cardiac effects, the clinical actions of ephedrine and dopamine are apparently unchanged.[212,213] Depth of anesthesia or responses to noxious stimuli may be difficult to assess due to a normally elevated baseline HR and delayed CO and HR responses. Therefore, BP responses may provide a more accurate guide to anesthetic requirements. Both atrial and ventricular dysrhythmias are common findings in the recently transplanted heart, due to: (1) the presence of coronary artery disease; (2) episodes of acute rejection; and (3) as an incidental finding in the long-term heart transplant patient. Ventricular dysrhythmias may be due also to a lack of suppressant vagal tone, increased endogenous catecholamine concentrations, and/or hypersensitivity to catecholamines.[198,214] Supraventricular dysrhythmias occur frequently, possibly due to surgical trauma of the sino-atrial node, ischemia, or as a consequence of a rejection episode.[215] These dysrhythmias respond to treatment with standard antidysrhythmic drugs, cardioversion where appropriate, and correction of an underlying rejection episode with large doses of immunosuppressive drugs.[216] For treatment of tachydysrhythmias, some evidence suggests adenosine supersensitivity of the denervated human heart.[217]

Only direct-acting pharmacologic agents will have predictable inotropic or chronotropic responses. Any maneuver or drug that relies solely on reflex autonomic neural pathways for its chronotropic effect will not produce a change in HR, i.e. M-muscarinic-1 and M2 agonist (fentanyl, phenylephrine), M1 and M2 antagonist (atropine, glycopyrrolate, meperidine), M2 antagonist (pancuronium) or cholinergic, M2 agonist (neostigmine, edrophonium, pyridostigmine). However, peripheral actions on vascular tone are maintained.[218]

Sodium thiopental may produce greater hypotension than expected, due to its intrinsic myocardial depressant action, and absence of reflex increase in HR. Opioids may not be as effective in the treatment of "light anesthesia" because of their inability to decrease HR and BP via vagal mechanisms.[219] Nitrous oxide can produce unanticipated hypotension because of the lack of its sympathetic stimulating properties to offset its direct myocardial depressant effect.[220] Isoflurane can also produce exaggerated hypotension due to an absence of reflex increases in HR in response to vasodilation.[219] Reflex tachycardia, often seen with vasodilator drugs used to treat preeclampsia (hydralazine, glycerin trinitrate, and sodium nitroprusside), is absent and hypotension may be exaggerated.[110] Caution should be exercised in the administration of ergonovine or PGF_2-alpha for uterine hypotonia. Although no cases of angina pectoris have been reported in a pregnant transplant patient, EKG monitoring for coronary ischemia during labor and delivery is essential. Three years post heart transplant, at least 30% of patients will have significant single or multivessel coronary artery disease in the transplanted heart.[100]

Use muscle relaxants with minimal histamine-releasing and ganglionic-blocking properties (see Table 22.17).[219] Neostigmine has been reported to produce bradycardia and sinus arrest in heart transplant patients, which could be explained by cholinergic receptor hypersensitivity, direct activation of cardiac ganglionic cells, vagal reinnervation, or sinus node dysfunction from surgical trauma, ischemia, or rejection.[221,222] If muscle relaxants are required, recommendations include administration of short- or intermediate-acting agents (cisatracurium, mivacurium) with ventilation of the patient until spontaneous recovery of muscular function occurs without attempting reversal of neuromuscular blockade.[221] Both external and internal pacemakers, atropine, and beta-adrenergic agonists (isoproterenol or epinephrine), should be readily available to treat bradydysrhythmias in heart transplant patients undergoing general anesthesia.[222]

The immediate sympathetic response to laryngoscopy and intubation should be absent. Other maneuvers such as externalization of the uterus producing vagal stimulation and reflex bradycardia with hypotension, would not be expected to occur.[196]

Table 22.17 General anesthesia for cesarean section: a suggested technique for heart transplant patients

External and internal pacemakers, atropine, and β-adrenergic agonists such as isoproterenol or epinephrine, should always be readily available.

1. Administer aspiration, steroid, and antibiotic prophylaxis
2. Volume preload with dextrose-free crystalloid (or colloid) solution, preferably two indwelling intravenous catheters
3. Position supine (left uterine displacement), surgical preparation, and draping
4. Noninvasive monitors: EKG, automatic blood pressure cuff, pulse oximetry, neuromuscular blockade (invasive monitoring for renal, respiratory, or cardiac compromise)
5. Preoxygenation ($O_2 > 6$ liters/min)
6. Assistant readiness to apply cricoid pressure, surgeon poised
7. Rapid sequence induction with cricoid pressure: thiopental 4 mg/kg or propofol 2 mg/kg and succinylcholine 1.5 mg/kg, careful intubation of trachea within 60 seconds, verify cuffed endotracheal tube placement with end-tidal CO_2 monitor and chest auscultation prior to releasing cricoid pressure. Do not precurarize the patient, due to interaction potential of magnesium, CyA, and nondepolarizing muscle relaxants
8. Maintenance: nitrous oxide 50%, isoflurane <0.75%
   - Choice of muscle relaxants: no additional relaxant, mivacurium, or cisatracurium (do not administer reversal dose of neostigmine and atropine, document sustained head lift for five seconds prior to extubation and again in recovery room)
9. Hypotension (systolic blood pressure <100 mmHg or decreased by 30%): determine etiology, ensure LUD, administer fluids, ephedrine 5–15 mg i.v., isoproterenol (avoid maternal hyperventilation and high peak inspiratory pressures)
10. With delivery of the baby, deepen anesthesia with narcotics and benzodiazepines, continue isoflurane <0.50%/N_2O/O_2, limit FiO_2 to 40% in heart–lung transplant patients
11. Extubate with the patient fully awake; demonstrate adequate ventilation, oxygenation and recovery from residual muscle relaxant

Table 22.18 Regional anesthesia for cesarean section: a suggested technique for heart transplant patients

1. Administer aspiration prophylaxis.
2. Volume load with 1 to 2 liters of dextrose-free crystalloid (or colloid) solution.
3. Administer supplemental oxygen, apply hemodynamic monitors (blood pressure cuff, EKG, pulse oximetry), and position patient.

NOTE: Resuscitation equipment and drugs must be readily available for use.

Epidural anesthesia

Local anesthetic solutions:

1. 0.5% bupivacaine or 0.5% ropivacaine
2. 2% lidocaine
3. 3% chloroprocaine
   - Addition of epinephrine to a concentration of 1:200 000 for the test dose (15 μg) and fractionated incremental doses up to 20 ml is controversial.
   - Availability of a titratable infusion of esmolol and observation of heart rate with EKG monitoring is essential.
   - Adjustment for rapid onset with sodium bicarbonate (8.4%): 1:10 ml with lidocaine or chloroprocaine and 0.1:10 ml with bupivacaine/ropivacaine.
   - Addition of epidural narcotics for intraoperative analgesia recommended (fentanyl 50 to 100 μg) and morphine 3 mg following delivery.
4. Position patient supine with left uterine displacement.
5. Monitor arterial blood pressure every minute until delivery of the baby, then every five minutes for the duration of the block.
6. Anxiety or "patchy" anesthesia may be treated with: fentanyl 1 μg/kg, ketamine 0.25 mg/kg, midazolam 1–2 mg or nitrous oxide 40%, with additional intravenous narcotic following delivery.

Spinal anesthesia

Local anesthetic solutions:

1. Bupivacaine 10 to 12.5 mg (0.75% with 8.25% dextrose solution)
   - Avoid hyperbaric lidocaine solutions.
   - Optional addition of intrathecal narcotics including fentanyl 10 to 15 ug or preservative-free morphine 0.1 to 0.2 mg for postoperative pain relief.

Epidural analgesia is preferred for labor and delivery as incremental injection of local anesthetics and titration of the level of sympathetic blockade will allow time for volume loading and physiologic compensation by the patient (see Tables 22.18 and 22.19). One should be aware of the additional infection risk to the CNS when choosing epidural and spinal anesthesia.[87] The epidural catheter should not be left *in situ* for more than two days, as the incidence of infection increases after this time.[199] Complete sympathetic denervation implies that levels of regional anesthesia above T4 would not be expected to result in bradycardia.[223] Epidural injection of an epinephrine-containing local anesthetic in a patient with a transplanted heart produced a profound tachycardia, which has the risk of precipitating myocardial ischemia. The proposed mechanism for this exaggerated response was systemic absorption of epinephrine in the face of exquisite sensitivity of the transplanted heart to β-adrenergic agonists.[223] Others report intact alpha- and beta-adrenoreceptors in the denervated heart responding normally to circulating catecholamines without evidence of denervation hypersensitivity to exogenous and endogenous catecholamines.[213,224]

Postpartum monitoring includes: assessment of cardiovascular and renal status, temperature, fluid balance, evaluation of ventricular function with serial EKGs, echocardiography, and cardiac isoenzymes, plus cardiac biopsy if acute rejection is suspected.

All equipment used directly on the heart–lung(s) or lung transplant patients should be sterile and a disposable circuit with a bacterial filter should be used on the anesthetic machine.[110] Careful placement of the endotracheal tube with monitoring of FiO_2, arterial blood gases, (pulse oximetry, capnography, or invasive monitoring), peak airway pressures, and fluid infusions should minimize the risk of oxygen toxicity, barotrauma, or stress

Table 22.19 General considerations for management of the transplant recipient during labor and delivery

1. Mandatory strict adherence to aseptic techniques
2. Augmentation of steroids for labor-induced stress
3. Minimizing invasive monitoring techniques
4. Essential antibiotic prophylaxis for all invasive monitoring and instrumentation
5. Assessment and optimization of graft function
6. Anticipation of altered physiologic and pharmacologic responses in the denervated organ
7. Continuation of immunosuppressive therapy
   For patients not permitted oral intake, the oral to intravenous conversion factors for immunosuppressive drugs are:
   - Prednisone po: methylprednisolone i.v. – 1:0.8
   - Azathioprine po: azathioprine i.v. – 1:1
   - CyA po bid: CyA i.v. bid – 1:0.25, infused over 6 hours twice daily
8. Maintain surveillance and optimization of renal function, blood pressure, and fluid balance
9. Identify maternal problems related to the pregnancy, immunosuppressive therapy, transplant surgery, or coexisting systemic illness
10. Vaginal delivery is recommended, but cesarean section may be required in at least 50% of women

on the tracheal/bronchial anastomosis, excessive increases in pulmonary vascular resistance, and volume-overload of the lungs. Excessive secretions with sputum retention and ventilation/perfusion mismatch can be minimized with the use of antisialogs, suctioning, and humidification of inspiratory gases. Although 60% to 80% of both ventilation and perfusion will go to the new lung in single-lung recipients, the patient should be extubated with the native lung (or the least important lung during an episode of rejection or infection) in the dependent position.[112] In the absence of a cough reflex, extubate the patient when fully awake to minimize the risk of bacterial pneumonia. Encourage expectoration from the transplanted lung by postural drainage and physiotherapy.[110]

Despite denervation of vagal efferents, bronchoconstriction has been described in a patient with a transplanted lung, which subsequently rejected,[225] and following implantation of apparently normal lungs.[226] The response to bronchodilators such as isoprenaline, aminophylline, and epinephrine was poor. It has been noted that some heart–lung transplant patients have an increased $PaCO_2$ in the postoperative period, which decreases to within normal limits over time.[110] Concerns have been raised that drugs that depress ventilation may further obtund the response to carbon dioxide.[225] The clinical significance of this observation is not clear.

Volatile agents are well tolerated[210] and their use is preferable to either long-acting muscle relaxants, high-dose narcotics, or benzodiazepines, which may preclude early extubation.[112] Although i.v. preload with crystalloid is acceptable for heart recipients, a similar approach in lung transplant recipients may severely damage the organs, due to their extreme sensitivity to pulmonary leakage.[112] Monitoring of RV function is essential if there is evidence of residual pulmonary hypertension or cardiac decompensation.

Summary

During the past two decades organ transplantation has become widely accepted as an established therapeutic option for patients suffering from end-stage organ failure. The ultimate goal for these patients is not purely survival at all costs, but rather the resumption of a normal life style, which for many young women includes childbearing. Despite early concerns, at least 14 000 births among women with transplanted organs have been reported worldwide.[7] Pregnancy is now an expected part of the benefits afforded to women by organ transplantation. Important advancements in organ preservation and immunosuppressive therapy have drastically improved patient and graft survival, and as such it is inevitable that with increasing frequency the anesthesiologist will be requested to participate in the care of the pregnant transplant recipient during labor and delivery. This chapter has been compiled from a review of the literature, discussion among colleagues, and my personal experience as a transplant anesthesiologist.

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23 AUTOIMMUNE DISEASES

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Introduction

An autoimmune disease represents a pathological condition caused by an immune response directed against an antigen within the body of the host. The most accepted theory suggests that autoimmunity results from a failure of the normal regulation of the immune system (which contains many immune cells that recognize self antigens, but are normally suppressed).[1] The exact etiology of these diseases remains unclear, although there are a number of factors that are implicated in their development, including infection, hormonal effect, drug exposure, and human leukocyte antigen (HLA) type. The incidence and activity of autoimmune diseases are particularly high in young women and hence their occurrence in parturients is not uncommon. During pregnancy, mother and fetus produce immunological factors to limit cell-mediated immunity and prevent fetal rejection, but the high estrogen environment may enhance immune function resulting in these demographic findings.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic disorder characterized by symmetrical polyarthritis, resulting in joint destruction and deformity. Diagnosis depends on an aggregation of clinical symptoms, signs, laboratory data, and radiological data (see Table 23.1). The joints primarily affected include the wrists, knees, shoulders, and metacarpal-phalangeal joints, with frequent sparing of the larger joints and spinal column. However, RA is a multisystem disease and extra-articular manifestations include lymphadenopathy, fatigue, anemia, weight loss, interstitial lung disease, pericarditis, subcutaneous nodules (rheumatoid nodules), vasculitis, neuropathy, renal disease, Sjögren syndrome (parotid and lacrimal hypertrophy, keratoconjunctivitis, vaginitis, xerostomia), and Felty syndrome (see Table 23.2). The disease usually follows a slow progressive course with exacerbations and remissions, although prognosis is highly variable.

The prevalence of the disease is 1% in the USA with all races being affected.[2] The overall female-to-male ratio is approximately 3:1, increasing to 5:1 in the pregnant population.[3] The reason for this female preponderance is in part due to the effects of estrogen on the immune system (inhibition of T suppressor cell function, enhancement of T helper cell function).[4] In addition, receptor polymorphism may be associated with the disease as estrogen receptors have been found on synovial and memory T cells.[5] Rheumatoid arthritis is polygenic in inheritance with an increased incidence of RA in patients with the HLA-DR4 phenotype. Other risk factors include smoking, nulliparity, and being in the early postpartum period.[6] Women are less likely to develop the disease during oral contraceptive use or during prolonged breast feeding (>one year).[7,8]

The diagnosis of RA is usually based on the clinical pattern of joint involvement, presence of rheumatoid factor, and typical bony erosive x-ray changes (see Table 23.1). The autoantibody rheumatoid factor is found in 80–90% of patients with RA, although RA factor titers do not correlate with disease activity. Rheumatoid factor is not exclusive to RA and is found in patients with other autoimmune diseases and in some normal patients.[9]

Drug treatment for RA sufferers includes: analgesics (e.g. aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids), glucocorticoids (e.g. prednisolone), and antirheumatics (e.g. methotrexate, hydroxychloroquine, sulfasalzine, leflunomide, gold, D-penicillamine, azathioprine, and cyclosporine). The current treatment rationale employs a combination of agents from different drug classes to maximize efficacy whilst minimizing side effects.

Effect of pregnancy on rheumatoid arthritis

Approximately 75% of patients with RA improve during pregnancy, but not all studies confirm this.[10,11,12] Clinical characteristics, such as disease duration, rheumatoid factor titers, and functional class, do not predict the course of RA during pregnancy. However, similar patterns of disease change recur in individuals during future pregnancies.[13,14] In those patients with a reduction in symptoms, the improvement usually starts during the first trimester and continues throughout the course of pregnancy. Unfortunately, 90% of RA patients deteriorate to their antepartum status within three months postpartum.[13,15] Spontaneous and therapeutic abortions produce similar deterioration following delivery. There may be an increased risk of developing RA in this early postpartum period, especially in first-time mothers.[10] Some authors suggest that breast feeding may be a risk factor for developing RA,[16,17] but, as breast feeding occurs at a time when disease activity normally deteriorates, the actual effect is difficult to determine. In addition, the physical demands of caring for an infant may result in worsening fatigue, joint pain, and depression.[18]

Effect of rheumatoid arthritis on pregnancy

Rheumatoid arthritis probably does not affect biological fertility; however, there is a significant reduction in coital frequency and libido.[19] Fetal morbidity and mortality are not increased in RA parturients,[11,20] but one study found a slight increase in

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Table 23.1 Clinical features for diagnosis of rheumatoid arthritis

Morning stiffness for ≥one hour and present ≥six weeks
Swelling of wrist, metacarpophalangeal, or proximal interphalangeal joints ≥six weeks
Swelling of three or more joints for ≥six weeks
Symmetric joint swelling
X-ray changes to hand – must include erosions or bony decalcification
Rheumatoid nodules
Rheumatoid factor

spontaneous abortion.[21] However, these studies may be biased as parturients with severe disease may choose not to have children due to their reduced functional capacity.

A major concern in RA parturients is the potential risk from drug therapy (see Table 23.3). For commercial and ethical reasons, many drugs currently used to treat RA are not approved for use in pregnancy creating a dilemma for the obstetrician and anesthesiologist. Fortunately, improvement in RA symptoms during pregnancy may permit a reduction in medication dose and revision of combination therapy, reducing maternal and fetal side effects. Therapy during pregnancy should be directed at using the lowest effective dose and avoiding those drugs known to affect the fetus adversely. Clearly, where the evidence is inconclusive, the benefits of the drug should significantly outweigh any potential risks or a relatively safe alternative should be chosen.

Table 23.2 Anesthetic implications of rheumatoid arthritis

Organ	Disease process	Anesthetic implication
Airway	Mandibular hypoplasia	Possible difficult intubation
	Temporomandibular joint dysfunction	
	Cricoarytenoid arthritis	
	Laryngeal deviation	
Cervical spine	Subluxation	Avoidance of excessive manipulation during GA
		Use of alternative to direct laryngoscopy
Joints	Joint destruction/deformity	Care with positioning
		Additional padding
		Possible difficulty with IV placement
		Risk of TE (decreased mobility)
Lumbar spine	Calcification of ligaments	Regional techniques may be difficult
	Osteophytes	Paramedian approach may be easier
CVS	Pericarditis	Limited cardiac reserve
	Pericardial effusions	Conduction disturbances
	Myocarditis	Antibiotic endocarditis prophylaxis may be necessary
	Myocardial nodules	Increased risk of end-organ damage
	Endocardial vegetations	
	Atherosclerosis	
	Vasculitis	
RS	Pleural effusion	Limited respiratory reserve
	Pulmonary fibrosis	
	Pulmonary nodules	
	Costochrondritis	
Neurological	Peripheral nerve root compression	Awareness of neurological abnormalities prior to neuraxial anesthesia
	Cervical nerve root compression	
	Vasculitis/neurovascular disease	
Hematological	Anemia	Reduced oxygen transport
	Felty syndrome	Increased risk of infectious complications
	(RA and neutropenia, may be associated with anemia, thrombocytopenia, enlarged spleen)	Increased risk of spinal hematoma
Eye	Scleritis	Taping/padding during GA to avoid damage
	Episcleritis	

GA = general anesthesia; IV = intravenous; TE = thromboembolism; CVS = cardiovascular system; RS = respiratory system

Table 23.3 Drug therapy for rheumatoid arthritis in pregnancy

Drug	Maternal effects	Fetal effects
Aspirin	Prolonged gestation/ labor Bleeding	Bleeding Metabolic acidosis Premature closure of ductus arteriosus Pulmonary hypertension
NSAIDs	Prolonged gestation/ labor Bleeding	Bleeding Premature closure of ductus arteriosus Pulmonary hypertension Renal dysfunction
Glucocorticoids	Weight gain Cushingoid features Increased risk of infection Adrenal suppression Diabetes mellitus Hypertension Osteoporosis Aseptic necrosis of joints Depression Psychosis	? Cleft lip/palate Adrenal suppression
Hydroxychloroquine (antimalarial)	Retinopathy	? fetal ocular/ ototoxicity
Methotrexate	Hepatotoxicity Leucopenia	Craniofacial defects Limb defects CNS defects
Sulfasalazine	Blood disorders Neutropenia Thrombocytopenia	No fetal defects
Azathioprine	Nausea and vomiting Leukopenia Hepatotoxicity Impairment of fertility	? Intrauterine growth restriction Various fetal defects reported Teratogenic
Leflunomide	Renal impairment Bone marrow depression Diarrhea Hepatotoxicity	Teratogenic
Gold	Bone marrow depression	Congenital abnormalities unlikely
D-Penicillamine	Bone marrow depression Nephrotoxicity	Connective tissue abnormalities Cuta laxa Dislocated hips Hernias
Cyclosporine	Hypertension Nephrotoxicity/ hepatotoxicity Hirsutism Paresthesias/ tremors Anemia Gum hyperplasia Alopecia	

CNS = central nervous system; NSAIDS = nonsteroidal anti-inflammatory drugs

The mainstays of drug therapy for symptoms of RA are aspirin or NSAIDs, which are generally safe in pregnancy. Neither of these drug classes is teratogenic in humans; however, these agents should be avoided by women having conception difficulties as they prevent blastocyst implantation in animals.[22,23] Both aspirin and NSAIDs may increase the incidence and severity of maternal anemia, prolonged gestation and labor, and bleeding problems (e.g. hemorrhage).[18,24] In addition, potential adverse fetal effects include increased bleeding (e.g. neonatal cephalohematoma, intracranial hemorrhage in preterm infants), premature closure of the ductus arteriosus, pulmonary hypertension, impaired renal function, and oligohydramnios. Ideally, aspirin and NSAIDs should be avoided six to eight weeks prior to delivery to reduce the incidence of these problems. Significant plasma aspirin levels have been found in breast-fed babies, raising concerns of possible metabolic acidosis, altered pulmonary circulation, and Reye syndrome. Therefore, avoid high doses of aspirin in nursing mothers, although normal doses do not appear to cause major concerns. Nonsteroidal anti-inflammatory drugs are weak acids and are only minimally transferred to breast milk. Breast-feeding is considered safe in women on NSAIDs;[25] however, as NSAIDs can displace bilirubin from plasma proteins the nursing mother of a jaundiced neonate should avoid them due to the increased risk of kernicterus.

Corticosteroid therapy appears to be relatively safe in pregnancy, although there may be a slight increased risk of cleft palate and lip in the newborn, together with an increased risk of pre-eclampsia (PET), gestational diabetes, premature rupture of membranes, and intrauterine growth restriction (IUGR).[26] All corticosteroids cross the placenta but the shorter-acting agents (prednisone, prednisolone, methyl-prednisolone) are partially inactivated by placental 11-β-dehydrogenase. When these shorter-acting agents are used, the fetus is exposed to minimal drug concentrations. Administer the lowest effective dose of corticosteroids and avoid fluorinated preparations (dexamethasone, betamethasone) to reduce fetal exposure. This policy also minimizes any increased risk of neonatal adrenal suppression and infection. Breast-feeding is considered safe during maternal consumption of corticosteroids as only small amounts of the drug are seen in the breast milk.

Methotrexate and leflunomide are absolutely contraindicated in pregnancy due to teratogenic effects (craniofacial defects, limb

defects, anencephaly, hydrocephaly, meningomyelocele). As methotrexate may cause folate deficiency, supplemental folate should be given to avoid neural tube defects. Breast feeding is not recommended with methotrexate due to the risks of neutropenia, immunosuppression, and carcinogenesis. Similarly, azathioprine is best avoided in pregnancy due to its risk of teratogenicity. Infants exposed to azathioprine are at risk of anemia, leukopenia, thrombocytopenia, infections, reduced immunoglobulin levels, and thymic atrophy. Sporadic abnormalities associated with azathioprine use include polydactyly, pulmonary stenosis, atrial septal defect, and hypospadias, but causation has not been proven.[27] It should be noted that a large number of patients with renal transplants and inflammatory bowel disease have had successful fetal outcomes while taking azathioprine.[28] Patients requiring azathioprine should consider delaying pregnancy until disease improvement permits discontinuation of their medication. Penicillamine is associated with fetal connective tissue disorders (cuta laxa, hernias, dislocated hips, IUGR) and should be avoided in pregnancy.[29] Cyclosporine has not been associated with severe fetal adverse effects, but based on a few case reports there may be an increased risk of prematurity and spontaneous abortion. Sulfasalazine appears safe in pregnancy and in breast-feeding. There are no reports of fetal abnormalities,[30] but since sulfasalazine impairs folate absorption, supplemental folate should be given. Gold seems to have limited adverse fetal effects; however, the lack of studies probably should preclude its use during pregnancy and lactation.[24] Hydroxychloroquine and chloroquine are probably safe in pregnancy in normal doses. These drugs have been used in pregnancy for malarial prophylaxis and the treatment of rheumatic diseases with only one report of ocular and ototoxicity in three children of a mother with systemic lupus erythematosus.[27,31] If hepatic or renal dysfunction exists, care should be taken with the total dose.

Obstetric management

The parturient with RA should be managed using a multidisciplinary approach, involving obstetricians, anesthesiologists, neonatologists, and rheumatologists. As RA is a multisystem disease, all affected organs should be evaluated. Estrogen, progesterone, and relaxin cause ligamentous relaxation, which may place increasing strain on weight-bearing joints in RA parturients. In addition, as pregnancy progresses, the increasing uterine mass accentuates lumbar lordosis and compensatory thoracic kyphosis. The importance of correct posture and exercises to relieve discomfort should be emphasized. Vaginal delivery is the preferred method of delivery, and cesarean section (C/S) should be done for obstetric reasons.[32] In rare, severe cases the disease may pose a problem to the mechanics of vaginal delivery and severely diseased hips or lower spine may preclude the use of stirrups. Patients who have had hip replacements are at greater risk of dislocation and care should be taken to avoid excessive flexion or rotation of the hips. In patients taking corticosteroids, additional doses may be required during labor and delivery, due to possible suppression and atrophy of the hypothalamic-pituitary adrenal axis. However, this standard approach has been challenged in a study where additional corticosteroids were not given to elective, orthopedic surgery patients who were taking regular prednisolone.[33] There were no detrimental effects, but further studies are necessary to clarify this important issue.

Anesthetic management

The affected organ systems in RA that may influence anesthetic choice are summarized in Table 23.2. In particular, the preanesthetic assessment should focus on a careful evaluation of the airway and cervical spine as RA patients may have mandibular hypoplasia, temporomandibular joint (TMJ) dysfunction, cricoarytenoid arthritis, and/or neck problems (see Table 23.4). Examine the airway and document all findings even if the patient has no overt symptoms of airway involvement, as general anesthesia may become necessary for urgent delivery. Clearly in those patients known to have a difficult airway, an early epidural during labor is prudent to provide analgesia and allow instrumental or surgical delivery, if required.

MacArthur and Kleiman[34] recommended that all RA patients have cervical x-rays prior to elective surgery, as 80% of RA patients have cervical spine involvement. Symptoms of stiffness or discomfort, as well as limitation of cervical flexion and extension, should be noted. The majority of neck extension occurs at the atlanto-occipital joint, which has approximately 35° of extension in the normal patient. If this value is <23°, visualization of the trachea using conventional laryngoscopy may be difficult or impossible. The majority of flexion occurs between C3 and C6, with 40° flexion being normal.[35] If the patient is unable to flex or extend

Table 23.4 Effect of rheumatoid arthritis on airway access

Joint	Role in airway access	Effect of RA
Atlanto-occipital	Majority of neck extension	If <23° extension, direct laryngoscopy may be impossible, FOI may be necessary
Temporomandibular	Mouth opening Mandibular protrusion	Interincisor gap < 3 cm, or inability to protrude the mandibular incisors in front of the maxillary incisors is highly predictive of a difficult intubation. FOI may be necessary
Cricoarytenoid	Narrowest upper airway diameter	Cricoarytenoiditis may result in complete closure of vocal cords preventing passage of endotracheal tube (or air). Tracheostomy may be required.

FOI = fiberoptic intubation

her neck adequately, alternative techniques such as flexible, fiberoptic laryngoscopy are indicated.

Cervical joint destruction (atlantoaxial and subaxial – below C1–2) may result in instability and subluxation in 25–50% of patients with longstanding disease.[36] Other risk factors for subluxation include increased age at onset of disease, rapidly progressive erosive peripheral joint disease, increased activity of synovitis, presence of rheumatoid factor, and elevated C-reactive protein level.[37,38] Atlantoaxial subluxation can be demonstrated if the distance from the anterior arch of the atlas to the odontoid process is >3 mm on lateral cervical x-ray (in flexion). Neurological injury may arise if movement causes the odontoid process to compress the spinal cord or the vertebral arteries. An increased incidence of cord compression occurs when the distance between C1 and C2 is >9 mm, the posterior atlantodental distance is <14 mm or if the space available for the spinal cord is <13 mm anywhere in the cervical region.[39] Extreme care should be taken during intubation to minimize further displacement of the odontoid process by excessive movement of the neck. The "sniffing the morning air" position is widely recommended as the standard head and neck position (extension at occipitoatlantoaxial region and flexion at subaxial region) for conventional direct laryngoscopy. There is a report of worsening of anterior atlantoaxial subluxation with the sniffing position in an RA patient. Although no neurological consequences occurred, the authors recommended caution in using the sniffing position.[40] Concerns regarding application of cricoid pressure in patients with cervical subluxation are unfounded.

Campbell and colleagues[41] questioned the routine use of preoperative cervical x-rays in RA patients. In their study there was a 5.5% incidence of unsuspected C1–2 subluxation in 128 RA patients undergoing elective surgery. Twenty patients had documented craniocervical instability and, despite different airway management techniques, there were no reports of neurological damage. In order to diagnose cervical instability, the following x-rays are needed: lateral views of the neck in flexion and extension, an antero-posterior view of the cervical spine in addition to frontal "open mouth" view of the odontoid process of C2. These images may be difficult to interpret in advanced disease and magnetic resonance imaging (MRI) scans may be needed. Sagittal and axial images in both flexion and extension (functional MRI) are useful for demonstrating atlantoaxial and subaxial subluxation and the presence of cord compression.[42]

The TMJ can be assessed by noting any clicking, locking, or limitation of movement. Mouth opening involves two distinct motions of the TMJ: firstly, a hinge type action, allowing the mouth to be opened halfway, and secondly, a forward gliding of the condylar surface on the articular surface enabling full opening of the mouth. Normal mandibular opening in an adult requires both motions with normal values for interincisor gap > 3 cm.[43] Evaluation of the second motion of the TMJ may be accomplished by having the patient try to protrude the mandibular incisors in front of the maxillary incisors. The combination of an interincisor gap of <4–5 cm and the inability to protrude the mandibular incisors in front of the maxillary incisors is highly indicative of critically limited TMJ mobility[44] and the need for a different technique to secure the airway.

Cricoarytenoid joint involvement has been reported in 26–86% of RA patients.[45] Acute cricoarytenoid synovitis should be suspected if the patient has symptoms of hoarseness or throat discomfort/fullness that increases with phonation, coughing, or swallowing, pain or tenderness over the larynx, or inspiratory stridor. Patients with chronic cricoarytenoid arthritis may be asymptomatic at rest, but several rapid, deep inspirations may reveal occult stridor. Airway decompensation can occur with infection or laryngeal manipulation. Flexible fiberoptic pharyngo-laryngoscopy can be used to evaluate cricoarytenoid joint mobility but caution is warranted as the joints may be red and swollen, and pregnancy may cause additional edema and narrowing of the airway. Traumatic examination may result in acute, complete airway obstruction.[46,47] The use of a smaller than usual endotracheal tube is recommended with mild to moderate cricoarytenoid involvement; however, with severe laryngeal disease, consultation with an otorhinolaryngologist is necessary. If a regional anesthetic technique is not possible, the patient may require a tracheostomy to secure her airway prior to surgery.

One report[48] described awake, fiberoptic intubation in a parturient with Still disease following failed regional anesthesia for C/S (see Table 23.5). Additional personnel, capable of assisting in the management of failed intubation, and special airway equipment should be available for these patients. It may be better to secure the airway via a primary tracheostomy in patients with severe cricoarytenoid arthritis, rather than risk laryngeal trauma after several failed intubation attempts. An otorhinolaryngologist should be informed of the patient's status and be on standby, if necessary. After extubation, monitor for symptoms of glottic obstruction, secondary to cricoarytenoid inflammation.

About 10% of RA patients have Sjögren syndrome (keratoconjunctivitis sicca due to lacrimal dysfunction and reduced tear formation), and require special attention to prevent corneal injuries, especially if a general anesthetic is required. Similarly, dysfunction of the salivary glands can result in a dry mouth, making the mucosa more vulnerable to damage after instrumentation.

Patients with RA are particularly susceptible to injuries caused by improper positioning. Arrangements should be made for additional supports and/or padding before beginning any anesthetic. The neck and lower back should be well padded and supported, and extensive hip flexion or rotation avoided.

Table 23.5 Problems with awake, fiberoptic intubation in parturients with rheumatoid arthritis

1. Fetal side effects of maternal sedative drugs
2. Risk of aspiration of stomach contents (especially as pregnant patients known to be at risk of regurgitation) following topical local anesthesia
3. Risk of severe hemorrhage (due to nasal engorgement during pregnancy) if nasal fiberoptic intubation used
4. Coughing following airway manipulation/topical local anesthesia. Potential neurological consequences in patient with cervical subluxation

Regional anesthesia is not contraindicated in RA parturients. A paramedian approach to the spinal canal may be easier if the interspinous ligament is calcified or osteophytes are present.

Postpartum management

Approximately 90% of RA patients deteriorate in the early postpartum period so antirheumatic medications may have to be reintroduced or dosages increased.[15] The choice of medication has to be balanced against risks associated with breast feeding. Prednisone and NSAIDs are probably the best choices as these are considered safe in breast feeding. Despite an increased prevalence of depression in RA patients compared with the general population, there is no evidence of increased postpartum depression.[49] However, additional support for the mother is important as reactivation of the disease, in addition to the demands of a new baby, may cause considerable problems.

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus is a chronic inflammatory disease of unknown etiology. Patients with SLE show a great diversity of signs and symptoms making diagnosis from similar disorders difficult. Prevalence is reported as 40–50 cases per 100 000 of the population and this figure is thought to be increasing, probably related to improvements in diagnosis.[2] Systemic lupus erythematosus has a mean age of onset of 25 years and is commoner in nonCaucasians with an adult female to male preponderance of 10–15:1, making it the commonest of the collagen vascular diseases seen in pregnancy.[50] Although the etiology of SLE is unknown, it is clearly multifactorial, with hormonal (e.g. estrogen), genetic (e.g. HLA B8, DR2, DR3 haplotypes), immunological, and environmental (viruses, ultraviolet light) factors contributing to the initiation and progression of the disease. Clinical effects are mediated directly or indirectly by antibody formation and/or the deposition of immune complexes. The American College of Rheumatology proposed a list of criteria to establish the diagnosis of SLE,[51,52] where four or more of the criteria are necessary to meet the entry requirements for clinical studies. However, only one of the classical clinical signs plus immunological findings (antinuclear and anti DNA antibody measurements) is sufficient for the clinical diagnosis of SLE.[53] Antinuclear antibodies, anti-double-stranded DNA antibodies, and antibodies to extractable antigens (e.g. antiRo, antiLa antibodies) are found in 90%, 80%, and 30% of SLE patients respectively. The commonest disease pattern includes a mixture of constitutional complaints (e.g. fatigue, fever, weight loss) together with musculoskeletal (e.g. arthralgia, arthritis), skin, mild hematological, and serological involvement. However, some patients experience predominantly renal, central nervous system (CNS), or hematological manifestations (see Table 23.6).

The clinical course of the disease is highly variable and characterized by relapses and remissions. Exacerbations may be precipitated by ultraviolet light, infections, drugs, or pregnancy. Prognosis is related to the severity of the disease and the degree of organ involvement. Factors associated with increased morbidity and

Table 23.6 Diagnosis of systemic lupus erythematosus[51,52]

Criterion	Definition
Malar rash	Fixed erythema over malar eminences, often with sparing of nasolabial folds
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Arthritis	Nonerosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion or Pericarditis – documented by EKG, rub, or evidence of pericardial effusion
Renal disorder	Persistent proteinuria > 500 mg per day (or >3 + on dip stick if quantization not performed) or Cellular casts (may be red cell, hemoglobin, granular, tubular or mixed)
Neurological	Seizures or psychosis (in the absence of offending drugs or known metabolic derangements – uremia, ketoacidosis, or electrolyte imbalance)
Hematological	Hemolytic anemia (with reticulocytosis) or Leukopenia (<4 000/mm^3 total on two or more occasions) or Lymphopenia (<1 500/mm^3 on two or more occasions) or Thrombocytopenia (<100 000/mm^3 in the absence of offending drugs)
Immunological	Positive antiphospholipid antibody or AntiDNA (antibody to native DNA in abnormal titer) or AntiSm (presence of antibody to Sm nuclear antigen) or False positive serological test for syphilis known to be positive for at least six months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug induced lupus" syndrome

EKG = electrocardiogram

earlier onset of organ damage include Hispanic ethnicity, greater disease activity, and a history of thrombotic events.[54] Poor survival prognostic factors in SLE patients include renal disease (particularly diffuse proliferative glomerulonephritis), male sex, hypertension, poor socioeconomic class, black race, high disease activity, presence of antiphospholipid antibodies (aPLs), and secondary antiphospholipid syndrome (APS).[55,56] Approximately 6% of women with SLE will have a coexisting autoimmune disease, most commonly secondary APS.

Effect of pregnancy on systemic lupus erythematosus

Although pregnancy does not seem to affect the long-term outcome of SLE, its impact on acute exacerbations remains uncertain[57] because of the normal spontaneous fluctuations of the condition. However, the majority of studies suggest the disease deteriorates in pregnancy.[20] Two prospective studies showed a significant increase in the rate of flares in pregnancy, with mostly constitutional, articular, and cutaneous manifestations.[58,59] In contrast, another study found no detrimental effect on the disease.[60] Rates of exacerbations of SLE during and after pregnancy range from 13.5–65%.[59,61,62] Flare frequency increased with greater disease activity at time of conception, lower serum albumin, proteinuria, and the use of prednisolone and hydroxychloroquine.[62,63] Clearly, these risk factors may represent patients with more severe disease. Patients who conceive during active SLE or in the presence of lupus nephritis have a 50% probability of serious exacerbations during their pregnancies.[64,65] Approximately 10% of SLE patients with preexisting renal involvement will develop permanent renal dysfunction.[13] If mild exacerbations are included, some worsening will occur in 48% of all pregnant SLE patients, 33% of these in the postpartum period. The incidence of flares during the immediate postpartum period can be reduced by giving corticosteroids during labor.[13] Termination of pregnancy has no beneficial effects on either the acute exacerbations of lupus or the long-term course of the disease.[64]

Effect of systemic lupus erythematosus on pregnancy

Systemic lupus erythematosus does not affect fertility in the absence of active disease, renal failure, treatment with high-dose steroids, or cyclophosphamide therapy.[66,67] The incidence of permanent amenorrhea following cyclophosphamide treatment ranges from 11–59% and is increased with age and cumulative dose.[68] However, SLE does lead to increased maternal and fetal morbidity and mortality.

Effect on mother

Parturients with SLE have an increased risk of preeclampsia (PET), which ranges from 5–38% in reported studies.[67] Distinguishing between PET and nephritic lupus flare may be difficult, but important, as treatment regimes differ (i.e. delivery for PET, immunosuppressive therapy for nephritic flare). Both conditions can cause proteinuria, hypertension, and worsening renal function, although the presence of active urinary sediment (white cell, red cell, or granular casts), reduction of C3/C4, and disease activity in other organs, favor the diagnosis of a lupus nephritic flare.[67] Risk factors for developing PET in these patients include renal disease, aPLs, preexisting hypertension, diabetes mellitus, and preexisting thrombocytopenia.[69] Other potentially lethal complications of SLE include severe lupus nephritis, severe serositis, cerebritis, adult respiratory distress syndrome, and pulmonary hemorrhage. Although pulmonary hemorrhage occurs in only 2% of patients with SLE, young women, and hence the parturient population, are at increased risk.[70] Mortality and morbidity from this complication remain high and largely result from respiratory failure and major blood loss. The efficacy of available therapeutic options has not been fully evaluated due to lack of randomized controlled trials. Keane and coworkers[71] described alveolar hemorrhage in a parturient with SLE which was refractory to treatment with steroids and azothiaprine and necessitated the use of cyclophosphamide. Despite treatment, respiratory failure and recurrent alveolar hemorrhage only resolved after termination and delivery of a nonviable fetus.

Effect on fetus

Patients with SLE have an increased rate of fetal loss (spontaneous abortion, stillbirth) compared to the normal population. Reported fetal loss has ranged from 20–30%[62] and increases in patients with aPLs, low levels of pregestational serum albumin, and high disease activity.[62,72,73] Other fetal risks include IUGR and prematurity.[62,73,74] Long-term effects seen in children born to SLE mothers include an increased risk of learning disabilities in male offspring.[75] As well there is a risk of neonatal lupus, a passively acquired autoimmune disease resulting from transfer of maternal autoantibodies to Ro/SSA, La/SSB, or U1RNP antigens.[76] Less than 33% of babies of women positive for these antibodies develop neonatal lupus. Approximately 50% of the babies affected will manifest classical skin lesions of lupus and approximately 2% will develop congenital complete heart block.[77,78,79] Neonatal lupus is responsible for up to 90% of cases of congenital heart block in the neonatal period.[80]

Rarely, other organ systems are involved in neonatal lupus, resulting in hemolytic anemia, thrombocytopenia, leukopenia, hepatosplenomegaly, or glomerulonephritis. Most of the manifestations of neonatal lupus resolve completely within the first six months of life, with the exception of heart block, for which 50% require cardiac pacing.[77] Complete heart block is thought to result from either antibody attack on fetal cardiac conductive tissues, immune complex deposition in myocardial tissue, or as a consequence of fetal myocarditis. Complete congenital heart block is usually diagnosed by fetal echocardiogram after 18 weeks' gestation. Glucocorticosteroids, NSAIDs, and plasmapheresis are ineffective in altering the course of the fetal cardiac outcome.[77] However, there is a suggestion that the early use of dexamethasone may reverse myocarditis and possibly heart block.[81] Prediction of those fetuses at risk for developing complete congenital heart block is difficult, as mothers of affected infants are often asymptomatic at the time of presentation.[76,77]

Medical management

The cornerstone to successful management of SLE parturients is to reduce or prevent end-organ damage. This is challenging during pregnancy as the additional physiological and metabolic demands imposed by the fetus may compromise already dysfunctional maternal organs. A multidisciplinary approach, involving obstetricians, anesthesiologists, neonatologists, and rheumatologists is useful to improve care of these patients. Activity of SLE can be assessed by a combination of clinical history, examination, and serological studies.[82] Numerous serological markers (e.g. antinuclear antibodies, anti-double-stranded DNA antibodies, aPLs, extractable nuclear antibodies – anti-Ro, anti-La, complement levels, erythrocyte sedimentation rate, C reactive protein) have been used to assess disease activity, although they are not necessarily specific or sensitive.[83]

The essential areas of treatment are described in Table 23.7. Many of the drugs used for this condition are also used to treat RA and are described earlier. As NSAIDs may be inappropriate in patients with renal dysfunction, antimalarial medication can be used successfully to treat SLE patients. Hydroxychloroquine is considered safe during pregnancy and continuation of therapy during pregnancy is probably safer than risking increased SLE exacerbations. Stopping hydroxychloroquine after pregnancy has been confirmed, will not avoid fetal exposure as the drug has a long elimination half-life. Breastfeeding should be used with caution due to slow drug elimination and the possible accumulation of toxic doses in the neonate.[22] Corticosteroids with or without immunosuppressive drugs are generally reserved for patients with significant organ involvement particularly renal or CNS disease. Sulfonamide antibiotics and penicillin (but not semisynthetic penicillins) should be avoided as anecdotal reports suggest that they may increase disease exacerbations. Other drugs, e.g. hydralazine, and procainamide, known to cause drug-induced SLE, are safe in the idiopathic form of the disease.

Women with SLE have a nine to tenfold increase in risk for coronary artery disease associated with accelerated atherosclerosis. Thus, patients with SLE and traditional risk factors for coronary artery disease should be managed aggressively using medication, diet, and lifestyle modification.[84]

Table 23.7 Treatment for systemic lupus erythematosus

Nonsteroidal anti-inflammatory drugs (NSAIDs)
For symptomatic relief of arthritis and arthralgia
Antimalarial drugs (e.g. hydroxychloroquine)
For rashes and arthritis
For flares
Glucocorticosteroids
For severe flare or lower doses for maintenance
Immunosuppressive drugs
For severe flare (often in combination with corticosteroids)
Additional treatment
Antibiotics for infection
Thromboprophylaxis
Antihypertensives if needed
? Anticonvulsants for cerebral disease

Obstetric management

Close vigilance of the parturient with SLE is vital, as these patients are at high risk for associated conditions, in addition to organ deterioration. Obstetric management should begin with an assessment of baseline clinical state and disease markers to assess prognosis and to detect any deterioration at a later stage. Initial investigations include: full blood count, platelet count, urea, electrolytes, uric acid, autoantibody screen (e.g. antiRo, anti La antibodies), anticardiolipin antibody (aCL), lupus anticoagulant (LA), complement levels (C3, C4, CH50), urinalysis, and 24-hour urine protein. Platelet count and creatinine should be measured monthly. Any deterioration of SLE or symptoms of PET require a full blood count, platelet count, urea, electrolytes, creatinine, uric acid, and urinalysis (plus 24-hour urinary protein). Close consultation between the obstetrician and rheumatologist is necessary throughout the pregnancy. Anti-double-stranded DNA antibodies may or may not be present during inactive SLE, but increase markedly prior to flares, and remain elevated for up to two weeks.[53]Antiphospholipid and aCLs in SLE patients are associated with an increased risk of fetal loss and maternal thrombotic complications. Ro/SSA and La/SSB antibodies are associated with an increased risk of neonatal lupus and fetal congenital heart block.

Monitor fetal growth and development from early pregnancy through delivery to reduce morbidity and mortality. If the mother has autoantibodies to Ro/SSA or La/SSB antigens, a pediatric cardiology consultation is indicated as early as 20 weeks' gestation to rule out fetal cardiac involvement. Consultation with other specialists is dictated by the specific organ systems affected by the disease. Clearly, it is prudent to consult with the anesthesiologist and neonatologist as the fetus nears 24 weeks' gestation, since early emergency delivery may become necessary.

Vaginal delivery is preferred, but delivery mode should be tailored to maternal and fetal conditions. Although the ideal timing of delivery is at term, worsening renal function, hypertension unresponsive to treatment, or fetal distress may necessitate preterm delivery. Supplementation of corticosteroids may be necessary during labor and delivery in those patients on regular corticosteroid treatment. Because of immunosuppression, close vigilance for signs of infection is important and prompt treatment necessary. In addition, both mother and neonate should be monitored in the postpartum period for flares and neonatal lupus respectively.

Anesthetic management

Full evaluation of all associated organ disorders is important (see Table 23.8). Although arthritis occurs in approximately 90% of SLE patients, the spine and hips are rarely affected and therefore positioning during labor and regional anesthesia are rarely a technical challenge. Cardiac abnormalities occur in over 50% of SLE patients and include pericardial, myocardial, valvular, and coronary artery disease.[85] Signs and symptoms of cardiac disease should be noted and routine electrocardiogram (EKG) performed (plus echocardiogram, if necessary). A structural valvular disorder is the commonest cardiac abnormality in SLE, with mitral regurgitation being the

Table 23.8 Clinical features and anesthetic implications of systemic lupus erythematosus

Organ	Disease problem	Anesthetic implications
NS	Cognitive dysfunction (20–80%)	Consent issues
		Differential diagnosis of PET/treatment
	Seizures (10–20%)	
	Risk of stroke (<15%)	Possible need for thromboprophylaxis (problems with regional and insertion)
	Psychiatric conditions	
	Peripheral neuropathy (10–15%)	Neurological assessment should be made prior to regional insertion
Skin	Epidermal and subdermal lesions	Minimal
Lungs	Pleuritis	Pain
	Pneumonia (increased risk)	Care with sterility, antibiotics if appropriate
	Fibrotic lung disease	Respiratory impairment
	Pulmonary hypertension (rare)	Oxygen/vasodilators
Kidney	Glomerulonephritis Lupus nephritis	Renal dysfunction/ altered drug handling
CVS	Increased risk of cardiac disease: (pericardial, valvular, myocardial, coronary artery disease)	Depends on abnormality
		May require endocarditis prophylaxis
	Cardiac abnormalities (50%)	
GIT	Dysphagia (<25%)	Risk of aspiration
	Risk of mesenteric vasculitis/infarction	Risk of acute abdomen
	Risk of peptic ulcer	
Hematological	Anemia	Reduced oxygen carrying capacity
	Leukopenia	Risk of infections
	Thrombocytopenia	Concerns with insertion of regional techniques
	Antibodies to clotting factors/ phospholipids	Abnormalities in in vitro coagulation tests
		Problems in cross-matching blood

NS = nervous system; CVS = cardiovascular system; GIT = gastrointestinal system; PET = preeclampsia

most frequent problem.[86] In one study, 51% of SLE patients had thickening, 43% vegetations, 28% regurgitation, and 4% stenosis of the mitral valve.[87] A five-year review found that nearly 25% of SLE patients had significant cardiovascular complications.[87] Pericardial involvement is common, but usually is benign, although almost 50% develop a pericardial effusion. Myocarditis is uncommon and often asymptomatic, although conduction abnormalities have been noted in 34–70% of SLE patients.[85] Occasionally, myocardial ischemia or infarction resulting from coronary artery vasculitis or accelerated atherosclerosis may occur in young women.[88] Risk factors for coronary artery disease in association with SLE include: increased age at diagnosis, increased duration of SLE, and longer duration of corticosteroid use.[89] Prophylactic antibiotics should be given to all parturients with known cardiac structural abnormalities during delivery, and anesthesia should be tailored to maintain cardiovascular stability.

Neurological and psychiatric (e.g. anxiety, mood disorders, psychosis, cognitive dysfunction) abnormalities occur in 10–80% of SLE patients. Approximately 15% of SLE patients have a peripheral neuropathy with sensory, rather than motor nerves, more likely to be affected.[90] Peripheral neuropathy is usually mild, asymmetric and affects more than one nerve (mononeuritis multiplex).[91] Autonomic neuropathy has been reported occasionally. Any neurological deficit should be noted and documented prior to regional anesthesia. Seizures occur in 10–20% of SLE patients and it may prove difficult to differentiate between SLE seizures and eclampsia.[92]

Radiological investigations of the chest may be utilized to evaluate the pulmonary complications of SLE, which include interstitial pneumonitis, pulmonary hemorrhage, pulmonary hypertension, and pleural effusion. Arterial blood gas analysis is indicated if pulmonary or cardiac involvement is suspected. Pulmonary function tests in patients with SLE may show a restrictive pattern with decreased vital capacity and diffusion capacity. Winslow and coworkers found that pulmonary hypertension developed in nearly 50% of SLE patients over a five-year period.[93] The diagnosis of pulmonary hypertension should be considered in patients who complain of dyspnea, chest pain, and nonproductive cough in addition to confirmatory physical signs (jugular venous distension, prominent A/V wave pulsations, hepatomegaly, ascites, peripheral edema). Anesthesia for parturients with pulmonary hypertension is discussed in Chapter 1. Successful general anesthesia has been reported in a parturient with SLE restrictive lung disease and pulmonary hypertension.[94]

The parturient with SLE must undergo hematologic evaluation. Although mild thrombocytopenia (platelet $100–150 \times 10^9$/l) has been noted in up to 50% of patients, platelet counts $< 50 \times 10^9$/l (precluding the use of neuraxial anesthesia) are found in only 10% of patients.[95] Antibodies to a number of clotting factors, including VIII, IX, XII, and XIII have been reported in SLE patients and may result in significant coagulopathy, again precluding the use of regional anesthesia. In patients with "lupus anticoagulant" – the term is a misnomer as its presence promotes thrombosis – there is an artifactual in-vitro prolongation of the activated partial thromboplastin time (aPTT), despite normal or increased in vivo coagulation. Antibodies to other phospholipids (e.g. aCLs) in moderate

or high levels can produce a similar effect. In these circumstances, the elevated aPTT does not suggest an increased bleeding tendency and regional anesthesia is not contraindicated.

Atypical antibodies can make typing and cross-matching of blood difficult and time consuming. Therefore, any patient at risk of significant hemorrhage should have early blood typing or cross-matching.

Systemic lupus erythematosus patients should be monitored carefully for signs of PET in the postpartum period. Those who are positive for aPLs or aCLs are at increased risk for thrombosis, and should have additional prophylactic thromboprophylaxis measures instituted immediately after delivery.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a rare multisystem autoimmune disease affecting about 6 per 100 000 individuals in the United States.[57] Unlike other collagen diseases, men are affected two to three times as frequently as women with a peak age incidence of between 40–60 years.[96] Due to the peak age of onset and the male preponderance, pregnancy with PAN is a rare occurrence. Although the etiology of PAN is unknown, it is thought to be autoimmune in origin, as antibodies and complement components have been seen in histochemical analysis of the lesions. Most cases are idiopathic, although there may be a link with hairy cell leukemia and hepatitis B virus (HBV) infection.[97,98]

Polyarteritis nodosa is characterized by a segmental necrotizing angiitis affecting mostly small- and medium-sized arteries, with a predilection for arterial bifurcations.[53,96] Affected areas dilate to form small aneurysms. During the acute phase, the media of the affected areas undergoes fibrinoid necrosis and infiltration with polymorphonuclear leukocytes and eosinophils. The patient is at risk of thrombosis, aneurysmal rupture, and infarction during this stage. Edema of the walls of the affected areas may result in complete occlusion of the vessel.

The acute phase gives way to a transitional phase, in which monocytes replace the polymorphonuclear leukocytes, and granulation tissue replaces areas of necrosis. Finally, during the chronic phase, scar tissue replaces former areas of necrosis, resulting in thickening of vessel walls and perivascular fibrosis. This proliferation of scar tissue and fibrosis may result in vessel occlusion. A characteristic feature is the coexistence of acute and chronic changes, often within adjacent sections of a vessel.[96]

The most commonly affected systems in PAN are skin, peripheral nerves, kidney, and gastrointestinal tract, but involvement of the lungs, CNS, and myocardium also occurs (see Table 23.9).[53,96,99] Diagnosis is made using the criteria devised by the Royal College of Rheumatology, which include unexplained weight loss (>4 kg), testicular pain in men, livedo reticularis, myalgia, mono/polyneuropathy, new onset hypertension (diastolic blood pressure [BP] > 90 mmHg), raised serum creatinine, evidence of HBV infection, characteristic arteriographic abnormalities (multiple aneurysms in larger vessels, occlusion of small penetrating arteries), and characteristic biopsy of small/medium sized artery of affected organs.[100]

The clinical presentation of PAN is one of constitutional symptoms such as fever, weight loss, arthralgia, and malaise, together with signs and symptoms of other organ involvement (see Table 23.9). Abdominal symptoms occur frequently, including anorexia, nausea, pain, diarrhea, and bleeding. Cardiac and renal involvement are common, leading to hypertension and myocardial infarction. Optimal treatment and duration of therapy remains unclear. The mainstays of therapy include corticosteroids and immunosuppressants (cyclophosphamide, azathioprine).[101,102] Antiviral therapy may be helpful in those patients with HBV-related PAN in order to diminish the immunosuppressant enhanced viral replication. Otherwise therapy is aimed at normalizing associated hypertension, in addition to supportive treatment of affected organ dysfunction. Renal transplantation in PAN patients is associated with a lower renal survival than in patients with other causes for end-stage renal disease.

Table 23.9 Clinical features of polyarteritis nodosa (Lhote)[99]

Clinical feature	Frequency (%)
Constitutional symptoms (fever, weight loss, fatigue)	70
Neuropathy (polyneuropathy, rarely cranial nerves affected)	65
Cutaneous (livedo reticularis, purpura, ulcers, bullous/vesicular eruption)	50
Arthralgias/myalgias	50
Renal disease (glomerulonephritis, raised creatinine)	50
Gastrointestinal symptoms (abdominal pain, rectal bleeding, diarrhea, nausea, vomiting)	40
Hypertension (new onset)	25
Respiratory manifestations (infiltrates, nodules, cavities)	25
Central nervous system disease (stroke, confusion)	20
Orchitis (testicular pain, swelling)	20
Myocardial manifestations (angina, myocardial infarction, cardiac failure)	10

Untreated patients with multisystem disease have a one-year survival < 50%, and a five-year survival of only 13%.[96,103] However, with current treatment, five-year survival is approximately 80%.[101] Poor prognostic features include renal and gastrointestinal involvement,[104] with mortality usually related to mesenteric, cerebral, or myocardial infarction or renal failure.

Impact of pregnancy on polyarteritis nodosa

Due to the limited number of case reports of PAN in pregnancy it is difficult to draw any valid conclusions about the effects of pregnancy on PAN. In the first six cases reported, all six women died within 33 days of delivery, and the finding of PAN was made at autopsy.[53] The first reported case of maternal survival occurred in 1970 in a woman who was diagnosed eight years before and had been treated with corticosteroids. Her fetus died in utero and was delivered by C/S. Of the six patients reported since 1970, one died 22 weeks post conception, following a spontaneous abortion at 20 weeks' gestation; one died 18 months postpartum; and the

Table 23.10 Clinical features and anesthetic implications of polyarteritis nodosa

Organ	Disease problem	Anesthetic implications
NS	Mononeuritis multiplex	Full neurological evaluation needed prior to regional insertion
	Asymmetric polyneuropathy	
	Occasionally cranial nerve neuropathy	
	Increased risk of ischemic CVA, intracerebral hemorrhage	Avoid cardiovascular instability, ameliorate pressor responses
Skin	Livedo reticularis, skin ulcers, bullous or vesicular eruptions, purpuric/petechial lesions (vasculitis)	Careful handling of patients Caution with regional if purpuric/petechial lesions
	Severe manifestations including infarction of fingers/toes	
Lungs	Interstitial lung disease	Respiratory impairment
Kidney	Glomerulonephritis	Renal dysfunction/altered drug handling
	Renal arterial aneurysms	Hypertension
CVS	Increased risk of IHD	Depends on severity
GIT	Abdominal pain, nausea/vomiting	Risk of aspiration
	Diarrhea, GIT bleeding	Dehydration Anemia (reduced oxygen carrying capacity)
	Risk of mesenteric vasculitis/infarction	Risk of acute abdomen
ENT	Epistaxis	Avoid nasal intubation if possible
	Sore throat	Careful airway management

NS = nervous system; CVS = cardiovascular system; GIT = gastrointestinal system; ENT = ears, nose, and throat; CVA = cerebral vascular accident; IHD = ischemic heart disease

remaining four survived.[53,96,105] Friedman and coworkers[53] speculated that patients with disease in partial or total remission at the onset of pregnancy have a better prognosis than those whose disease first occurs during pregnancy or the early puerperium. It is important to point out, however, that their analysis includes those six patients reported prior to 1970, in which the diagnosis was not made until autopsy. Only one of those patients received corticosteroids.

Impact of polyarteritis nodosa on the neonate

It is remarkable that nine of the thirteen (69%) reported pregnancies resulted in surviving neonates. There was only one intrauterine fetal death, two induced abortions, and one spontaneous abortion (at 20 weeks' gestation).[53,96,105] All neonates, except one who had vasculitis, were healthy.[106]

Termination of pregnancy does not appear to ameliorate disease activity and is not indicated for maternal PAN. The implications of maternal drug treatment (e.g. corticosteroids, azathioprine, cyclophosphamide) on the fetus and neonate are discussed in the section on RA.

Anesthetic management

There are no case reports addressing the issue of anesthetic management of PAN patients. Clearly it is important to involve other specialists, such as cardiologists and nephrologists depending on the clinical picture (see Table 23.10). Baseline investigations such as full blood count, urea, electrolytes, EKG, 24-hour urinary protein, and creatinine clearance are useful. The clinical picture may be similar to that of PET, so it is prudent to obtain baseline clotting studies (prothrombin time, aPTT, fibrinogen level, platelet count) and uric acid levels. Epidural analgesia is not contraindicated unless the patient presents with extensive purpura or has a coagulopathy. Careful documentation of any neurological deficit is important prior to any regional technique. Wide fluctuations of BP should be avoided as these patients may have multiple small aneurysms as well as areas of diminished blood flow secondary to intimal fibrosis and occlusion. Look for signs and symptoms of myocardial ischemia and evaluate complaints of chest pain or dyspnea. Supplementation with corticosteroids may be necessary during labor and delivery in those patients on regular corticosteroid treatment. As most of the deaths in PAN patients result from cardiorespiratory failure, renal failure, or gastrointestinal hemorrhage, it is sensible to focus postpartum monitoring on these areas.

Scleroderma (systemic sclerosis)

Scleroderma is a diverse, progressive, multisystem condition linked by the presence of thickened, sclerotic skin lesions.[107] Clinical manifestations occur in the skin, musculoskeletal, nervous, cardiovascular, pulmonary, renal, and gastrointestinal systems. Prevalence ranges from 4 to 253 cases per million individuals with a female-to-male preponderance of 3:1.[2] As the peak age of onset occurs in the fourth decade, scleroderma is relatively uncommon in pregnancy. However, the incidence of parturients with the disease is increasing as greater numbers of women opt to have children later in life.

The etiology and pathogenesis of scleroderma is not fully understood, although genetic and environmental factors may play a role. Most theories suggest a complex interplay between

immunological events and vascular changes resulting in activation of fibroblasts. Excessive collagen and other extracellular matrix constituents are produced leading to obliteration and fibrosis within the skin and other target organs.[108]

Scleroderma can be classified into three main subgroups and diagnosis is based on the presence of typical skin lesions, extracutaneous manifestations, and characteristic antibodies (see Table 23.11). The combination of skin lesions plus one or more of the following – hypertension (acute onset), renal deficiency, heartburn/dysphagia (new onset), telangiectasias (face, lip, hand), diarrhea with malabsorption, dyspnea on exertion (with radiological interstitial pulmonary changes), or pulmonary hypertension – strongly suggests the diagnosis.

The most common feature of scleroderma is Raynaud phenomenon, which is due to arterial vasoconstriction and results in characteristic sequential color changes to the hand (white, blue, and red). Permanent arterial insufficiency may result from structural damage to the vessel wall. Skin manifestations include edema, hyperpigmentation, skin thickening/hardening, skin tightening followed by atrophy and contractures. Changes usually occur initially in the hands and face but may be widespread, although the back and buttocks are usually spared. Dilated blood vessels (telangiectasias) commonly occur, particularly in the oral and nasal cavities. Cardiac disease results from fibrosis and sclerosis of the myocardial/conducting tissue and coronary vessels, in addition to indirect effects from pulmonary and systemic hypertension. Patients with symptomatic cardiac involvement have a 75% five-year mortality rate.[109] Life threatening or severe "scleroderma related renal crises" occur in 10–15% of patients and consist of a sudden onset of severe hypertension, progressive renal insufficiency, and microangiopathic hemolysis. Pulmonary involvement is also a major cause of morbidity and results from interstitial pulmonary fibrosis, which may lead to pulmonary hypertension. Peripheral and cranial neuropathy may result from compression of thickened adjacent connective tissue. Disease manifestations in the musculoskeletal system are edema, arthralgia, and myalgia.

Table 23.11 Classification of scleroderma

Limited cutaneous scleroderma
Long history of Raynaud phenomenon
Skin involvement limited to mostly hands (some on face, feet, and forearms)
Nail-fold capillary dilatation
10–15% late onset of pulmonary hypertension, telangiectasias, or interstitial lung disease
Renal involvement rare
May suffer from CREST syndrome (**C**alcinosis, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasia)
Anticentromere antibodies (70–80%)
Diffuse cutaneous scleroderma
Short history of Raynaud phenomenon before appearance of other skin changes
Widespread skin involvement particularly over proximal limbs and trunk
Nail-fold capillary dilatation
Early and significant involvement of renal, pulmonary, gastrointestinal, and myocardial disease
No anticentromere antibodies
Anti DNA topoisomerase I (Scl-70) antibodies, anti RNA polymerase I, II, III antibodies
Scleroderma sine scleroderma (rare)
No skin involvement
Visceral organs involved only (renal, pulmonary, gastrointestinal, and myocardial disease)
Raynaud phenomenon may be present
Antinuclear antibodies may be present

A multifaceted approach should be used in the treatment of the disease. Immunomodulatory and antifibrotic methods do not alter long-term progression of the disease, although glucocorticoids and cyclophosphamide may be useful in patients with alveolitis, myositis, arthritis, and serositis. Recombinant human relaxin (a heterodimer protein secreted by the corpus luteum and placenta during pregnancy) reduces skin thickening and improves motility in patients with moderate to severe diffuse scleroderma.[110] Otherwise, treatment should be directed at the individual organs involved.

Life expectancy is significantly reduced in patients affected by the disease, mostly as a result of renal failure and malignant hypertension. Poorer prognosis is associated with greater skin involvement, visceral disease (particularly cardiac, pulmonary, and renal), presence of antitopoisomerase I (anti-Scl-70), anemia, and elevated erythrocyte sedimentation rate.[111,112] Patients with the CREST variant (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) are thought to have a relatively benign disease and therefore a better prognosis. Increased risks of cancer, particularly lung tumors, are reported in patients with scleroderma.[113]

Effect of pregnancy

Most studies report that fertility is unaffected by scleroderma, although some suggest that it may be reduced.[114,115,116] The impact of pregnancy on scleroderma is difficult to quantify as many symptoms of pregnancy are similar to those occurring with the disease (e.g. gastrointestinal reflux, edema, dyspnea). The most important determinants of adverse maternal and fetal outcomes in parturients with scleroderma are the extent and severity of organ involvement. Pregnancy is safest in those patients without significant cardiac, pulmonary, or renal disease. Steen[117] prospectively reviewed 59 parturients (91 pregnancies) with scleroderma during a ten-year period. Symptoms remained unchanged during 63% of pregnancies, worsened in 18% (including deterioration in esophageal reflux, cardiac dysrhythmias, arthritis, skin thickening, and renal function), and improved (symptoms due to Raynaud phenomenon) in the remaining 20% of pregnancies.

Patients with hypertension or renal disease have a significantly increased risk of preeclampsia (PET) and frequent antenatal monitoring of BP is important.[20] Due to diagnostic difficulties in

distinguishing between scleroderma-induced renal crises, PET, and hemolytic uremic syndrome, it is unclear whether there is an elevated risk of sclerodermal renal crises in patients affected by the disease. However, in those developing renal deterioration during pregnancy, there is significant morbidity.[118] Although angiotensin-converting enzyme inhibitors are generally contraindicated in pregnancy due to associated fetal renal insufficiency, the benefits of these medications may outweigh their risks in the treatment of scleroderma-related hypertensive and renal crises.[119] Renal crises are the most common cause of maternal death in parturients with scleroderma. Steen[117] suggested that those with early diffuse scleroderma should consider avoiding pregnancy until their disease is stabilized in order to diminish the risk of renal complications.

Many studies suggest that there is an increased risk of spontaneous abortion in parturients with scleroderma,[120] with higher rates of loss seen in patients with diffuse rather than localized cutaneous disease. There may be an increased rate of premature and "small for gestational age" births but these studies are unclear about the influence of medications (particularly immunosuppressive agents) and other risk factors for prematurity.[115,121]

Obstetric management

Parturients should be evaluated fully and followed closely throughout pregnancy with input from cardiologists, nephrologists, and chest physicians. Close fetal surveillance is also important with attention given to the possible fetal effects of medications (see Table 23.3).

Vaginal delivery is the preferred method of delivery. However, ineffective uterine contractions or cervical dystocia during labor may result from uterine and cervical wall thickening.[115] Augmentation of labor with oxytocics should be used cautiously as considerable hemodynamic changes can occur. These changes may be detrimental in scleroderma patients with cardiac disease or pulmonary or systemic hypertension. Careful positioning of patients during delivery is important due to associated contractures and restrictive skin changes. Patients should be kept warm in order to reduce symptoms of the Raynaud phenomenon. Renal function should be monitored in patients with renal insufficiency. Moore and coworkers[122] reported an interesting case of obstructive uropathy resulting from uterine enlargement within a noncompliant abdomen.

Elective C/S may be required if fibrosis of perineum and cervix prevents vaginal delivery.[123] Wound healing may be problematic in patients with advanced disease and in those on corticosteroids, and a careful operative technique to promote healing is important. Patients with significant cardiovascular, pulmonary, or renal compromise would benefit from observation in a high dependency setting in the postpartum period.

Anesthetic management

Patients should be reviewed early in pregnancy so that organ involvement can be evaluated and anesthetic strategies formulated. Anesthetic implications and problems of scleroderma are

Table 23.12 Clinical features and anesthetic implications of scleroderma

Organ	Disease problem	Anesthetic implications
Skin	Nonpitting edema	Difficulty with cannulation
	Hidebound skin	Easy insertion of regional needles, due to sparing of lumbar area Difficult intubation (poor mouth opening)
CVS	Raynaud phenomenon	Caution with arterial cannulation as may result in digital ischemia
	Myocardial ischemia Chronic pericardial effusion	Reduced cardiac reserve
	Conduction disturbances	Risk of dysrhythmias
	Hypertension	Maintain cardiovascular stability
Respiratory	Interstitial fibrosis Pleural effusion Chest wall restriction	Limited respiratory reserve
	Pulmonary hypertension	Avoid precipitants producing increased PVR (hypoxia, hypercapnia, acidosis, pain, hypothermia, high positive end expiratory pressure)
GIT	Hypomotility	
	Reflux esophagitis	Risk of aspiration
	Diarrhea/ malabsorption	Dehydration Coagulopathy (vitamin K deficiency)
Renal	Proteinuria	Confusion with diagnosis of preeclampsia
	Renal insufficiency	Altered drug handling
	Malignant hypertension	Risk of end-organ damage
NS	Peripheral/cranial neuropathy	Full neurological evaluation needed prior to regional anesthesia
MS	Arthritis Myopathy Contractures	Adequate padding/ careful patient positioning

CVS = cardiovascular; GIT = gastrointestinal tract; PVR = pulmonary vascular resistance; NS = nervous system; MS = musculoskeletal system

described in Table 23.12. Venous access may be difficult due to cutaneous changes and central venous catheterization may be necessary. Noninvasive BP monitoring is the preferred technique, as arterial cannulation may induce vasospasm and distal necrosis. Brachial arterial catheterization may be superior to radial arterial catheterization in patients with the Raynaud phenomenon due to diminished ischemic risk.

The airway should be assessed, as difficulty with endotracheal intubation can be caused by limited mouth opening due to surrounding skin and connective tissue changes. Taut skin may also diminish neck mobility and hardening of the tissue in the submental triangle may limit the ability to align the oral, pharyngeal, and laryngeal axes during laryngoscopy.[124,125] In addition, the presence of oral and nasal telangiectasias should be noted as dilated capillaries may bleed profusely if traumatized. Extreme care should be taken during airway manipulation in these circumstances.

Early epidural analgesia for labor[124] is advised especially in those patients with a potentially difficult intubation, as this allows the block to be extended if C/S is required. The skin of the lumbar region is frequently spared from cutaneous involvement making regional needle insertion easy. Eisele and Reitan[126] found scleroderma patients have an increased sensitivity to local anesthetics and suggested the use of reduced doses of these agents. The use of slow incremental doses of local anesthesia via an epidural or intrathecal catheter is the technique of choice as it enables the anesthesiologist to titrate the dose of local anesthetic to the desired level. Single-shot spinal anesthesia for C/S was reported in a parturient with scleroderma, severe PET, thrombocytopenia, and a potentially difficult airway.[127] Intraoperative complications included precipitous hypotension and a high sensory block (to T2) following intrathecal bupivacaine and diamorphine. Prolonged duration of local anesthetics have been reported by several authors[124,126,128,129] and may result from diminished intravascular uptake due to disease-associated microvascular changes.

The successful use of general anesthesia[125,130,131] for C/S in scleroderma patients has been reported. Hseu and coworkers[130] administered an opioid-based general anesthetic for C/S in a scleroderma patient complicated by pulmonary hypertension secondary to restrictive lung disease. General anesthesia was chosen to enable airway control and hemodynamic stability with the aid of a pulmonary artery catheter.

The risk of aspiration in affected patients is greater than in normal parturients as gastric hypomotility is compounded by the normal physiological gastrointestinal changes that occur in pregnancy. Administer histamine-2 blockers during labor in case urgent C/S becomes necessary. The decision to use either regional or general anesthesia for C/S depends on the airway, urgency of delivery, and the presence of a functioning epidural. In patients with a potentially difficult airway, the decision for a C/S should be made early to enable adequate time for an awake fiberoptic intubation. As a result of decreased tear production in affected patients, hydrating ointments and eye pads should be used to protect against corneal damage.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by medium to high titers of antibodies directed against phospholipid binding plasma proteins, together with typical clinical manifestations of thrombosis or fetal loss.[132] However, due to variable organ involvement, clinical features are diverse (see Table 23.13). Cervera and coworkers[133] found that the commonest clinical manifestations reported in a series of 1000 patients with APS were deep vein thrombosis (32%), thrombocytopenia (22%), livedo reticularis (13%), cerebrovascular accident (13%), superficial thrombophlebitis (9%), fetal loss (8%), transient ischemic attack (7%), and hemolytic anemia (7%). Both venous and arterial thromboses occur, although venous thrombosis is more frequent than arterial. Occasionally patients can present with "catastrophic antiphospholipid syndrome" (CAPS), which represents a severe form of the condition associated with multiorgan failure secondary to thrombosis.

Antiphospholipid syndrome can either be primary (not associated with any underlying disease) or secondary (associated with SLE or another autoimmune/rheumatic disease). The three most commonly elevated aPLs associated with this condition are anticardiolipin (aCL), lupus anticoagulant (LA), and anti β2 glycoprotein I antibodies.[134] Low titers of aPLs are also found in healthy individuals, particularly the elderly, and they can be induced by infection or malignancy. Increased aPLs titers are also associated with SLE (23–47% of SLE patients have aCLs, 30% have LA, and 20% have antibodies to β2 glycoprotein I)[135] and other autoimmune diseases (e.g. RA, idiopathic thrombocytopenia).

Although thrombosis, infarction, and vasculopathy are thought to account for the majority of clinical features, the exact etiology

Table 23.13 Clinical features of antiphospholipid syndrome

Thrombosis (arterial/venous)	Deep vein thrombosis (calf is commonest venous site)
	Cerebral vascular accident (commonest arterial site)
	Mesenteric infarction
	Hepatic/renal thrombosis
Obstetric complications	Recurrent fetal loss
	Intrauterine growth restriction
	Preeclampsia
Skin	Livedo reticularis (reticular pattern of mottling over extremities or trunk)
Hematological	Hemolytic anemia
	Thrombocytopenia
Kidney	Nephropathy
	Thrombosis
Neurological	Seizures
Cardiac	Intracardiac/coronary thrombosis
	Mitral/aortic regurgitation (due to thickened valves)
Pulmonary	Pulmonary embolus
	Pulmonary arterial thrombosis
	Adult respiratory distress syndrome
Gut	Ischemic event

and pathogenesis remain unclear. Treatment of APS has been directed towards the prevention of thrombosis by the use of anticoagulants (heparin or warfarin) or antiaggregants (aspirin or clopidrogrel), or at the reduction of antibodies (immunosuppressives: corticosteroids, cytotoxic agents). However, the mainstay of treatment is anticoagulants, with immunosuppressive therapy reserved for those refractory to conventional treatment.

There is an increased risk of premature death in APS patients, although prognosis is variable. Mortality is related to the increased propensity to thromboembolism and the increased rates of malignancy, ischemic heart disease, adverse effects of anticoagulant medication, and associated diseases (e.g. SLE). Patients with differing subclasses of aPLs may have varying degrees of disease risk. Sammaitano and coworkers[136] found that patients with elevated titers of IgG aCLs (subclass 2) had an increased thrombotic risk compared with those having different aPLs. More than 50% of patients with APS who have experienced a thrombotic event will have a subsequent clinical thrombosis, and in approximately 70% the thrombosis will occur on the same side of the vascular tree.[137]

Development of CAPS results in a grave prognosis. There is a 50% mortality rate, and among survivors, 20% have further recurrent thromboembolic events despite anticoagulation.[138] Precipitating factors for CAPS include surgery (even minor operative procedures), infection, and the withdrawal of anticoagulants.[139]

Effect of pregnancy

Prevalence of aPLs in the normal obstetric population is approximately 5%[140] and 5–50% (mean 15%) in parturients with recurrent miscarriages.[134,141] Pregnancy compounds the already elevated risk of thrombosis in patients with APS. Additional pregnancy-associated complications of APS include infertility,[142] recurrent miscarriage (>10 weeks' gestation),[142,143] early severe PET, eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), thrombocytopenia, prematurity, stillbirth, and IUGR.[144]

The precise mechanism for fetal loss (>10 weeks' gestation) is unknown. However, it seems likely that the thrombotic risk of APS contributes to placental insufficiency. Paradoxically, APS may protect against recurrent early fetal loss (<10 weeks' gestation). One possible explanation is that in early normal pregnancy (<10 weeks' gestation) the trophoblast is exposed to reduced uteroplacental blood flow and low oxygen partial pressures, i.e. conditions that are normally found in patients with APS.

Although low-dose aspirin and heparin are recommended for parturients with APS, scientific evidence is weak, largely due to poor trial design and inter-trial clinical heterogeneity.[145] Benefits of low molecular weight heparin (LMWH) compared to unfractionated heparin (UFH) include better bioavailability, improved dosage regime, reduced risk of heparin-induced thrombocytopenia, and diminished risk of osteoporosis. There is no evidence to support the use of corticosteroids or intravenous immunoglobulin in affected parturients. Women on long-term warfarin anticoagulation should consider converting to heparin to avoid any potential teratogenic risks.

Anesthetic management

Two case series describe the anesthetic management of 20[146] and 27[147] parturients with APS. Both authors emphasized the likelihood of patients requiring anesthetic involvement. Of the 47 cases, 32 received regional anesthesia (22 epidurals, 5 spinals, 1 combined spinal–epidural) and 19 patients required C/S. Despite antithrombotic treatment, five patients experienced thrombotic episodes (including transient ischemic attack, pulmonary embolus, bilateral renal vein thrombosis, deep vein thrombosis) during pregnancy and the early postpartum period.

Parturients should be assessed early in pregnancy. Coexisting autoimmune disease (particularly SLE) and organ involvement should be evaluated. Patients with lupus anticoagulant (LA) have an artifactual in vitro prolongation of the aPTT, despite normal or increased in vivo coagulation. Clearly, regional anesthesia is not contraindicated in these cases. However, patients with APS may have significant thrombocytopenia, be receiving anticoagulant therapy, or rarely have antibodies to a number of clotting factors (including VIII, IX, XII, and XIII). This may result in significant coagulopathy and preclude the use of regional anesthesia. The development of thrombocytopenia in a parturient with APS may be due to PET, APS, or heparin-induced thrombocytopenia. In those patients receiving anticoagulation, the use of regional anesthesia is permitted once the coagulation profile has normalized after UFH (remember that the aPTT can be artificially raised in the presence of LA). For those receiving LMWH, 12 hours should have elapsed after the last thromboprophylactic dose (or 24 hours for those patients fully anticoagulated with LMWH). The advantages of regional anesthesia in a particular patient must be weighed against the small risk of a spinal hematoma.[148]

Atypical antibodies can make cross-matching and typing of blood difficult and time consuming. Therefore blood should be typed or cross-matched early in APS patients at risk of significant hemorrhage, or those with residual anticoagulant effect.

Patients with APS are at risk of thromboembolism, PET, and postpartum bleeding (due to anticoagulants or thrombocytopenia). Prophylactic antithrombotic measures, such as adequate hydration, early mobilization, and the use of antiembolic stockings, should be instituted as soon as feasible. Thromboprophylaxis or therapeutic anticoagulation (depending on the individual risk of thromboembolism) should be restarted (12 hours post C/S, 4–6 hours following vaginal delivery) and continued for at least six weeks postpartum. Long-term anticoagulation should be considered if thrombotic events are unrelated to the pregnant state.

Several case reports describe the problems associated with anesthetizing nonobstetric patients with CAPS.[149,150,151] The risks of opposing complications present an intraoperative challenge; catastrophic exacerbation of the thrombotic tendency may be triggered by the surgical stimulus and major bleeding may result from the necessary anticoagulation.

Summary

Autoimmune diseases are more frequent in the female population and hence their occurrence in parturients is not uncommon.

Specific conditions are variable in terms of disease activity and organs affected. The anesthesiologist should carefully analyze the disease impact in order to minimize deleterious outcomes during any medical intervention. In addition, the consequences of drug treatment on both the mother and fetus should be assessed.

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As the subject of this book is obstetric anesthesiology, all entries relate to this unless specifically stated.