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often viewed as convenient, efficient, and a common aspect of clinical care, without a comprehensive review of the record or any direct contact with the patient, curbside consults have been found to often be incomplete or even flawed. It is not uncommon for the question being asked to be deemed too complex for a curbside consult or for it not to be the actual or only issue the consultant feels needs to be addressed. As a general rule, curbside consults should be avoided. While medicolegal liability is often cited as a reason to limit curbside consults, the risk is actually negligible as U.S. courts have ruled that curbside consults do not establish a doctor-patient relationship necessary for creating the basis for medical malpractice litigation. An important exception, however, is when a curbside consult is provided by a resident or fellow in training; in this circumstance, the trainee's supervising physician, whether aware of the curbside consult or not, is responsible for the recommendations of the trainee.

Advice Related to curbside consultation, but decidedly different, are instances when one physician reaches out to another, often one in another specialty, for advice. Examples include an internist turning to a radiologist for guidance on what is the most appropriate imaging study to diagnose a deep tissue abscess; a general internist asking a gastroenterologist for advice on management of acute diverticulitis; a hospitalist asking a neurologist for guidance on management of a patient with Parkinson's disease who is NPO; or a nephrologist asking an infectious disease specialist about immunizations in a kidney transplant recipient. PART 19 Consultative Medicine Outreach such as this is typically triggered by a specific patient encounter, but the request is more for general information that the requesting physician may use for the encounter at hand as well as for similar encounters going forward. Thus, reaching out for advice differs from formal consultation and from curbside consultation, which are specific for a particular patient. As such, requests for advice fall within the realm of collegial communication and not necessarily within that of clinical consultation per se. Second Opinions Physicians may find themselves providing consultations requested by patients who have already been evaluated for the same problem by another physician. Not a "consult" in the usual context of one physician referring a patient to another, the service provided by the consultant is, nonetheless, very much aligned with a physician-referred consult. Second opinions, which often are encouraged by the patient's physician, may be sought by patients for

reassurance that a diagnosis and treatment recommendation are correct, out of dissatisfaction with the initial physician, or with the hope of an entirely different opinion and recommendation. The physician providing the second opinion should strive to understand the patient's motivations for seeking the additional opinion. While a second opinion may have been initiated by the patient rather than referral from another physician, it is recommended that the consulting physician communicate with the patient's primary physician, as would be done following a standard consultation, unless the patient insists otherwise. In addition, professional behavior in how the consulting physician refers to the recommendations or actions of previous physicians is important, including when there is disagreement. Likewise, it is important that a transfer of care from the prior physician to the one providing a second opinion be enacted only if specifically requested by the patient or the physician who encouraged the second opinion. Consults Involving Advanced Practice Providers Increasingly, specialist physicians may find themselves being consulted by nurse practitioners and physician assistants rather than other physicians. Whether the quality of the information provided to the consultant physician by these providers is different from physician-to-physician referrals has not been studied. Consulting physicians should know whether they should respond back to the advanced practice provider or to the supervising physician, if there is one. As with physician-to-physician consults, it is also important for the consultant to know whether the individual calling for the consult has an ongoing role in the care of the patient or is simply covering for a limited period of time. Finally, the consultant, if responding back to the advanced practice provider, should make sure that the information provided meets the

needs of that provider and that questions are answered as they would be if responding back to another physician. Consultation Involving Telemedicine and Electronic Health Records (EHRs) Consultations making use of EHRs, patient portals, and various forms of telecommunication technology, including video conferencing or cell phone communication, can improve access to care, reduce cost, and improve outcomes. This is particularly true when employed in geographic areas of health care shortage and when the clinical issues can be handled without direct contact with the patient, i.e., radiology or dermatology. However, the absence of direct contact between patient and consultant introduces special issues related to diagnostic accuracy and physician-patient relationship. Regulatory, liability, security, and confidentiality issues arise as well, as do concerns about disparities related to access to telemedicine technologies and willingness and ability to use them among some patient populations. ■ ■ FURTHER READING Ahmed S et al: Utility, appropriateness, and content of electronic consultations across medical subspecialties. A cohort study. *Ann Intern Med* 172:641, 2020. Pearson SD: Principles of generalist-specialist relationships. *J Gen Intern Med* 14:S13, 1999. Sulmasy DH: Policy recommendations to guide the use of telemedicine in primary care: An American College of Physicians Position Paper. *Ann Intern Med* 163:787, 2015. Sarah Rae Easter, Robert L. Barbieri

Medical Disorders

During Pregnancy Each year, ~3.7 million births occur in the United States, and >130 million births occur worldwide. A significant proportion of births are complicated by medical disorders. Advances in medical care and fertility treatment have increased the number of people with serious medical problems seeking pregnancy. Medical problems that interfere with the physiologic adaptations of pregnancy increase the risk for poor pregnancy outcome. Conversely, in some instances, pregnancy events may have implications for an individual's long-term health. HYPERTENSION (See

also Chap. 288) Cardiac output increases by 40% in pregnancy, with most of the increase due to an increase in stroke volume. Heart rate increases by ~10 beats/min during the third trimester. In the second trimester, systemic vascular resistance decreases, and this decline is associated with a fall in blood pressure. A blood pressure of systolic ≥ 140 and/or diastolic ≥ 90 mmHg on two measurements 4 h apart after 20 weeks' gestation is abnormal and is associated with an increase in perinatal morbidity and mortality. Hypertension during pregnancy is classified as preeclampsia, gestational hypertension, or chronic hypertension. These classifications are distinguished based on timing in pregnancy and the presence of associated features (see below). The prevalence of hypertensive disorders in pregnancy (HDP) is rising. The Centers for Disease Control and Prevention (CDC) estimated that in 2019, 16% of deliveries in the United States were complicated by a HDP. ■ ■PREECLAMPSIA Approximately 5–7% of all pregnant women develop preeclampsia, the new onset of hypertension (blood pressure $\geq 140/90$ mmHg) and proteinuria (either a 24-h urinary protein >300 mg/24 h or a

protein-creatinine ratio ≥ 0.3) after 20 weeks of gestation. Preeclampsia can be diagnosed without proteinuria in the presence of symptoms or laboratory abnormalities raising concern for end-organ damage. Specific clinical features qualify as evidence of severe disease, including severe hypertension (blood pressure $\geq 160/110$ mmHg), new-onset symptoms (headache not responsive to medications, visual changes, or unremitting severe epigastric pain), pulmonary edema, or laboratory abnormalities signifying thrombocytopenia (platelets $<100 \times 10^9/L$), renal insufficiency (creatinine >1.1 mg/dL), or liver impairment (elevation of transaminases to twice the normal concentration). Eclampsia is diagnosed when a pregnant person with preeclampsia develops generalized seizures. The HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) is a special subtype of preeclampsia with severe features and is a major cause of morbidity and mortality. Coagulopathy, cerebrovascular accidents (CVAs), hepatic capsule rupture, and placental abruption are additional end-organ complications of preeclampsia. The precise pathophysiology of preeclampsia remains unknown, but chronic uteroplacental ischemia, an exaggerated maternal inflammatory response, and/or imbalance of angiogenic factors likely contribute to the clinical syndrome. In preeclampsia, there is excess production of an antiangiogenesis factor, soluble fms-like tyrosine kinase 1 (sFlt-1), and decreased production of an angiogenic factor, placental growth factor (PlGF). A ratio of circulating sFlt-1/PlGF ≥ 40 is associated with an increased risk of developing preeclampsia with severe features in the 2 weeks following the measurement. Abnormalities of cerebral circulatory autoregulation explain some of the neurologic manifestations of the disease and can increase the risk of stroke at even modestly elevated blood pressures. In the absence of treatment, 1 in 100 cases of preeclampsia may progress to eclampsia—new-onset generalized tonic-clonic seizures in a patient with preeclampsia. Low-dose aspirin initiated between 12 and 14 weeks of gestation reduces the risk in women at high risk of developing preeclampsia. ■ ■GESTATIONAL HYPERTENSION The development of elevated blood pressure after 20 weeks of pregnancy in the absence of preexisting chronic hypertension or proteinuria is referred to as gestational hypertension. Gestational hypertension with severe features of the disease is best classified as preeclampsia. Both gestational hypertension and preeclampsia are associated with an increased risk of developing chronic hypertension, cardiovascular disease, chronic kidney disease, or diabetes mellitus later in life. TREATMENT Preeclampsia The management of preeclampsia is challenging because it requires the clinician to balance the health of the mother with the health of the fetus. The definitive treatment of preeclampsia is delivery of the fetus and placenta, but preterm delivery exposes the fetus to the risks of prematurity. In preeclampsia without severe

features, delivery at 37 weeks is recommended. People with preeclampsia without severe features may be managed expectantly until 37 weeks with close monitoring for development of severe features or laboratory abnormalities, frequent fetal surveillance, and limited physical activity to reduce blood pressure. Expectant management of preeclampsia with severe features remote from term affords some benefits for the fetus but at significant risk to the mother. For women with preeclampsia with severe features, delivery is recommended unless the patient is <34 weeks and eligible for expectant management in a tertiary hospital setting. Indications for delivery prior to 34 weeks include unremitting symptoms, development of laboratory abnormalities, or severe range blood pressures refractory to medical management. The goal of prolonging pregnancy to this gestational age is to improve neonatal outcomes. Therefore, concerns about fetal well-being, such as severe fetal growth restriction or placental abruption, may also prompt delivery before 34 weeks. Timely management of blood pressures $\geq 160/110$ mmHg reduces the risk of CVAs. Labetalol and

hydralazine IV are the first-line agents to manage severe hypertension in preeclampsia with consideration of oral agents once blood pressure is controlled.

Women who have had preeclampsia are at increased risk of cardiovascular disease later in life. Interventions to reduce cardiovascular risk can be initiated in health encounters following birth. ■
■ **CHRONIC HYPERTENSION** Pregnant people with chronic hypertension are at increased risk for superimposed preeclampsia and placental complications such as fetal growth restriction and placental abruption. These complications may necessitate preterm birth, which is associated with newborn respiratory distress syndrome. People with chronic hypertension should have a thorough prepregnancy evaluation to identify remediable causes of hypertension and to transition off antihypertensive agents associated with adverse outcomes in pregnancy. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are contraindicated in pregnancy because of an increased risk of stillbirth and congenital fetal anomalies. Labetalol and extended-release nifedipine are the most commonly used medications for the treatment of chronic hypertension in pregnancy. The optimal target blood pressure is <140/90 mmHg, which reduces the risk of developing preeclampsia and preterm birth. A preconception or early pregnancy assessment for end-organ impacts of hypertension, including the presence of proteinuria, may help differentiate the effects of chronic hypertension from those of superimposed preeclampsia. CHAPTER 491 ■
■ **RENAL DISEASE** Normal pregnancy is characterized by a 40% increase in glomerular filtration rate and creatinine clearance secondary to a rise in renal plasma flow. Patients with underlying renal disease may expect a worsening of existing hypertension or development of preeclampsia during pregnancy. A prepregnancy serum creatinine level ≥ 133 $\mu\text{mol/L}$ (≥ 1.5 mg/dL)

and low C4 levels are associated with adverse pregnancy outcomes. Certain pathologies, such as those associated with glomerular disease, increase the risk of adverse outcomes. Neither hemodialysis nor prior renal transplant is a contraindication to pregnancy, but both require close multidisciplinary management. When renal disease worsens during pregnancy, close collaboration between the internist and the maternal-fetal medicine specialist is essential so that decisions regarding delivery can be weighed to balance the sequelae of prematurity for the neonate versus long-term sequelae for the mother with respect to future renal function. Medical Disorders During Pregnancy **CARDIAC DISEASE** Cardiac disease is the leading cause of maternal mortality in the United States. Prepregnancy cardiac disease and cardiac disease caused by pregnancy are both

major contributors. Patient education, risk stratification, optimization of hemodynamics, and multidisciplinary planning with a pregnancy heart team are the tenets of management. Patients with pulmonary hypertension (Chap. 294), severe ventricular dysfunction (ejection fraction <30% or New York Heart Association class III–IV), severe mitral or aortic stenosis, severe aortic dilation, or Fontan circulation with severe complications are at the highest risk of maternal mortality. Pregnancy is contraindicated in these women, with termination of pregnancy as an option to reduce maternal risk. Risk stratification including a detailed history with attention to symptoms, echocardiography, and cardiopulmonary exercise testing guides monitoring and management for most patients. Contemporary guidelines support continuing most nonteratogenic prepregnancy medications and reserving cesarean delivery for obstetric indications with few exceptions. ■

■ **VALVULAR HEART DISEASE** (See also Chaps. 272–279.) **Mitral Stenosis** The pregnancy-induced increase in blood volume, cardiac output, and tachycardia can increase the transmitral pressure gradient and cause pulmonary edema or tachyarrhythmias in

women with mitral stenosis. People with moderate to severe mitral stenosis (mitral valve area ≤ 1.5 cm²) who are planning pregnancy and have either symptomatic disease or pulmonary hypertension should undergo valvuloplasty prior to conception, preferably with percutaneous balloon valvotomy. Careful control of heart rate and avoidance of hypovolemia, especially during labor and delivery, mitigate the risk of tachycardia and reduced ventricular filling times on cardiac function. The immediate postpartum period is a time of particular concern secondary to rapid volume shifts.

Aortic Stenosis People with aortic stenosis, a mean valve gradient <25 mmHg, and normal left ventricular function are likely to tolerate pregnancy. Symptomatic aortic stenosis or severe aortic stenosis with a peak gradient >50 mmHg should be evaluated for correction prior to pregnancy. **Mitral and Aortic Regurgitation** The pregnancy-induced decrease in systemic vascular resistance reduces the risk of cardiac failure with these conditions, especially in those with chronic lesions. As a general rule, regurgitant lesions are well tolerated in pregnancy with acute onset of mitral or aortic regurgitation as an exception. **Mechanical Heart Valves** People with mechanical heart valves are at high risk of valve thrombosis in pregnancy and warrant special consideration. Use of warfarin in pregnancy is limited to this population and avoided in the first trimester due to its association with fetal chondromalacia punctata. The risk of serious neonatal bleeding and associated neurologic injury persists throughout pregnancy, but the superiority of warfarin in preventing valve thrombosis merits its use in the second and third trimesters. Bridging from warfarin to heparin infusion at 36 weeks' gestation minimizes bleeding risk and facilitates neuraxial analgesia at delivery. **PART 19 Consultative Medicine** ■ ■ **CONGENITAL HEART DISEASE** (See also Chap. 280) Reparative surgery has markedly increased the number of adults with congenital heart disease seeking pregnancy with a variety of disease-specific management considerations and outcomes. Repaired septal defects are comparatively low risk, whereas unrepaired septal lesions or repaired complex lesions such as tetralogy of Fallot may warrant additional surveillance by a pregnancy heart team to ensure that pregnancy is tolerated. People with complications in the setting of lower risk disease or with high-risk disease including uncomplicated Fontan circulation, systemic right ventricle, or cyanotic disease require delivery at a tertiary care center with subspecialty expertise. In Eisenmenger's syndrome, i.e., the combination of pulmonary hypertension with right-to-left shunting due to congenital abnormalities (Chap. 280), maternal and fetal deaths occur frequently, informing the recommendation for termination of pregnancy. The presence of a congenital cardiac

lesion in the mother increases the risk of congenital cardiac disease in the newborn and is the basis for the recommendation to screen for fetal congenital heart disease with fetal echocardiography. ■

■ **AORTOPATHY** The physiologic cardiovascular adaptations of pregnancy can predispose to aortic dissection, the majority of which occur in people with underlying aortopathies (Chap. 291). Although dissection may occur in the absence of aortic root enlargement in some genetic syndromes, sequential transthoracic echocardiographic (TTE) monitoring during pregnancy for evolution of the aortic root diameter is the mainstay of monitoring those at risk. Aortic magnetic resonance imaging (MRI) without gadolinium is useful to define thoracoabdominal aortic pathology in high-risk diseases. For most diseases, an aortic root diameter <40 mm portends a favorable pregnancy outcome, whereas a diameter >50 mm is an indication for prepregnancy repair. Beta blockers are a mainstay of therapy for most patients. A high clinical suspicion for dissection in patients presenting with chest pain is mandatory. Marfan Syndrome (See also Chap. 425) This autosomal dominant disease is associated with an increased risk of aortic dissection and rupture. An aortic root diameter >40 mm is associated with an increased risk of aortic dissection, and an aortic root diameter >45 mm is

an indication for surgical treatment. Operative vaginal delivery to limit the aortic wall stress associated with Valsalva should be considered for women with an aorta of 40–45 mm. Ehlers-Danlos Syndrome (EDS) (See also Chap. 425) Vascular EDS (vEDS, type IV) is an autosomal dominant disease associated with an increased risk of uterine or vascular rupture that may cause death. For people with vEDS, pregnancy is relatively contraindicated because of this risk. ■

■ **CARDIAC COMPLICATIONS IN PREGNANCY** Arrhythmias New-onset arrhythmias in healthy patients or patients with cardiac disease are common cardiac complications. Treatment is generally the same as in the nonpregnant patient, and fetal tolerance of medications such as beta blockers, calcium channel blockers, and common antiarrhythmics is acceptable. Pharmacologic or electric cardioversion may be performed to improve cardiac performance and reduce symptoms according to standard indications. Peripartum Cardiomyopathy (PPCM) (Chap. 269) This uncommon but life-threatening condition should be considered in patients presenting in the third trimester or postpartum period with unexplained cardiogenic pulmonary edema. Treatment is directed toward symptomatic relief and improvement of cardiac function. The majority of patients recover completely. The subset of patients with left ventricular ejection fraction $<30\%$ are at high risk of progressive dilated cardiomyopathy. People with a history of PPCM may carry a genetic mutation that influences cardiac function. Approximately 10% of people with a history of PPCM have a truncating mutation in the titin gene encoding the sarcomere protein and experience higher rates of ongoing cardiomyopathy. Recurrence in a subsequent pregnancy is a risk, with a left ventricular ejection fraction of $<50\%$ 12 months post partum as the threshold to advise against another pregnancy. **ENDOCRINE AND METABOLIC DISORDERS** The fetoplacental unit induces major metabolic changes to shunt glucose and amino acids to the fetus while the mother uses ketones and triglycerides to fuel her metabolic needs. The use of glucose by the fetus leads to a maternal state of accelerated ketosis during maternal fasting, characterized by lower glucose concentrations and higher hydroxybutyrate and acetoacetate levels. These metabolic changes are accompanied by maternal insulin resistance that increases during the course of pregnancy caused in part by placental production of steroids, a growth hormone variant, and placental lactogen. ■ ■ **DIABETES MELLITUS** (See also Chaps. 415–417) Pregnancy complicated by pregestational diabetes mellitus (pgDM), either type 1 or type 2 diabetes, complicates $\sim 1\%$ of pregnancies and is associated with increased maternal and perinatal morbidity and mortality rates. The prevalence of pgDM is greater

among patients who are obese compared to normal weight (2.2 vs 0.5%). The metabolic changes of pregnancy can precipitate hyperglycemia requiring increased insulin needs, development of diabetic ketoacidosis, or hypoglycemia. Impaired glycemic control during the critical first 5–8 weeks of embryonic growth leads to an increased risk of spontaneous abortion and congenital malformations and highlights the importance of prepregnancy glycemic control. pgDM increases the risk of stillbirth, preeclampsia, and large for gestational age infants. Macrosomia increases the risk of shoulder dystocia and birth trauma, including brachial plexus injury and obstetric lacerations. Neonates are at risk of hypoglycemia, hyperbilirubinemia, polycythemia, and respiratory distress. An assessment of end-organ complications of pgDM including nephropathy, retinopathy, and neuropathy is essential to understanding the patient's risk profile. ■

■ **GESTATIONAL DIABETES** Gestational diabetes mellitus (GDM) occurs in ~8% of pregnancies, and screening for GDM is a routine part of prenatal care, recommended by the U.S. Preventive Services Task Force with a B recommendation. The typical two-step strategy to diagnose GDM is performed at 24–28 weeks of

gestation and involves the initial administration of a 50-g oral glucose challenge with a single serum glucose measurement at 60 min. Plasma glucose >7.2 mmol/L (>130 mg/dL) warrants administration of a 100-g oral glucose tolerance test (GTT) with plasma glucose measurements obtained in the fasting state and at 1, 2, and 3 h. Normal plasma glucose concentrations at these time points are <5.3 mmol/L (<95 mg/dL), <10 mmol/L (<180 mg/dL), <8.6 mmol/L (<155 mg/dL), and <7.8 mmol/L (<140 mg/dL) as the upper norms. Two elevated glucose values indicate a positive GTT diagnostic of GDM. GDM increases the risks of maternal and neonatal complications similar to those seen with pregestational diabetes. Treating GDM reduces the risk of preeclampsia, birth weight >4000 g, and shoulder dystocia. **TREATMENT Diabetes Mellitus in Pregnancy** Preconception counseling to optimize glycemic control and assess for end-organ complications of pgDM is a cost-effective and evidence-based intervention. Guidelines encourage people with pgDM considering pregnancy to initiate insulin prior to pregnancy, targeting a preconception hemoglobin A1c $<6\%$ to reduce the risk of fetal congenital malformation. Insulin is the preferred medical therapy for pgDM in pregnancy due to its safety profile and lower rates of treatment failure compared to oral hypoglycemic medications. Once pregnancy is established, glucose control should be managed more intensively than in the nonpregnant state with assessment of blood glucose when fasting and either 1 or 2 h after a meal at a minimum. Fasting blood glucose levels should be maintained at <5.3 mmol/L (<95 mg/dL), with postprandial targets of <7.8 mmol/L (140 mg/dL) or <6.7 mmol/L (120 mg/dL) at 1 and 2 h, respectively. Continuous glucose monitoring is an evidence-based intervention to improve neonatal outcomes in type 1 diabetes. Sequential measurement of hemoglobin A1c is of minimal utility for monitoring glucose control during pregnancy because of the higher rate of red blood cell turnover during pregnancy and resultant falsely low values. Average daily insulin needs increase from 0.7–0.8 units/kg in the first trimester to 0.8–1 units/kg in the second trimester and 0.9–1.2 units/kg in the third trimester. Most management strategies utilize a combination of basal insulin with short-acting insulin at mealtime or continued use of a prepregnancy insulin pump in appropriately selected patients. Glycemic control may become more difficult to achieve as pregnancy progresses due to an increase in insulin resistance. Attention to glycemic control and frequent fetal surveillance including ultrasounds are mainstays of management in the third trimester. Ultrasound identification of a large for gestational age fetus or polyhydramnios on antenatal ultrasound can be indicators of suboptimal glycemic control. Tight glycemic control at delivery minimizes the risk of neonatal

hypoglycemia due to fetal hyperinsulinemia caused by elevated maternal glucose levels. Infants of mothers with pgDM have higher rates of preterm birth, although preterm delivery is generally reserved for poor glycemic control, worsening maternal renal disease, or active proliferative retinopathy in addition to the usual obstetric indications. Induction of labor may be recommended in the early term period of 37–39 weeks of gestation. Cesarean delivery is reserved for cases of suspected macrosomia based on an estimated fetal weight of 4500 g or greater to minimize the risk of shoulder dystocia and associated birth trauma. **TREATMENT** Gestational Diabetes Treatment of GDM begins with nutritional therapy to optimize normoglycemia and gestational weight gain, which is effective in the majority of women. Insulin is the preferred therapy for patients who exceed the aforementioned targets despite nutritional therapy. Metformin and glyburide are alternatives for patients who decline

or cannot reliably take insulin. Contemporary data demonstrate lower mean birth weights, gestational weight gain, and rates of pre eclampsia with metformin compared to both glyburide and insulin. The unknown long-term developmental and metabolic effects of metformin, including higher adiposity measurements in children exposed to metformin in utero, inform the preference for insulin.

GDM confers a 7- to 10-fold increase in the risk of developing type 2 diabetes later in life, with a 10% risk within 5 years of delivery. All people with GDM should have a 2-h 75-g GTT to screen for diabetes or impaired glucose tolerance 4–12 weeks following birth. The increased long-term risks of diabetes and cardiovascular disease and the need for regular follow-up with a primary care provider should be emphasized for all people with GDM. Following birth, exercise, weight loss, and treatment with metformin reduce the risk of developing diabetes in these at-risk patients. ■

■ **OBESITY** (See also Chap. 414) Pregnant people who are obese have an increased risk for GDM, preeclampsia, cesarean delivery, congenital malformations, stillbirth, and neonatal death. A growing body of literature suggests the in utero effects of excess adipose tissue may cause changes in fetal metabolic programming that lead to adverse health outcomes in adult life. People contemplating pregnancy should attempt to attain a healthy weight prior to conception, recognizing that even a 10% reduction in weight may significantly reduce many of these risks. Those undergoing bariatric surgery should be counseled to avoid conception for 12–18 months after surgery until weight stabilizes. Bariatric surgery reduces the risks for some complications but requires increased laboratory surveillance for micronutrient deficiencies in pregnancy with appropriate supplementation. All women should be counseled to avoid weight gain in excess of the National Academy of Medicine guidelines (25–35 lb for normal weight, 15–25 lb for overweight, and 11–20 lb for obese women) with the knowledge that excess gestational weight gain increases the risk of macrosomia and cesarean delivery, independent of the presence of comorbid diabetes.

CHAPTER 491 Medical Disorders During Pregnancy ■ ■ **THYROID DISEASE** (See also Chap. 394) The estrogen-induced increase in thyroxine-binding globulin increases circulating levels of total T3 and total T4 in pregnancy. Placental human chorionic gonadotropin (hCG) directly stimulates the thyroid, causing an increase in free T3 and T4, especially in the first trimester. Interpretation of the measurement of free T4, free T3, and thyroid-stimulating hormone (TSH) should use trimester-specific ranges. People with a history of Graves' disease have an increased risk of fetal goiter and neonatal Graves' disease independent of treatment status due to the transplacental passage of thyroid-stimulating antibodies and stimulation of the fetal thyroid. **TREATMENT** Hyperthyroidism Options for the treatment of symptomatic hyperthyroidism in pregnancy include beta blockers,

propylthiouracil, and methimazole. Methimazole crosses the placenta to a greater degree than propylthiouracil and has been associated with fetal aplasia cutis. Propylthiouracil can be associated with maternal liver failure. Some experts recommend propylthiouracil in the first trimester and the option of continuing propylthiouracil or switching to methimazole thereafter. Radioiodine should not be used during pregnancy, either for scanning or for treatment, because of effects on the fetal thyroid.

TREATMENT Hypothyroidism The goal of therapy for hypothyroidism is to maintain the serum TSH in the normal range, and thyroxine is the drug of choice. The dose of thyroxine required to keep the TSH in the normal range

risks during pregnancy. Since the increased thyroxine requirement occurs as early as the fifth week of pregnancy, one approach is to increase the thyroxine dose by 30% (two additional pills weekly) as soon as pregnancy is diagnosed and then adjust the dose according to TSH.

HEMATOLOGIC DISORDERS Pregnancy has been described as a state of physiologic anemia. Red blood cell mass increases in pregnancy but to a lesser degree than plasma volume. This differential increase results in a lower hemoglobin concentration and so-called dilutional anemia. However, iron, folate, and vitamin B12 deficiencies are common causes of correctable anemia during pregnancy. Transfer of iron to the fetal compartment may explain why iron deficiency anemia is detected in ~11% of pregnant people in the third trimester. Screening for anemia is recommended in the first trimester and at 24 to 28 weeks' gestation. Measurement of ferritin can help detect iron deficiency before anemia is diagnosed. Iron replacement therapy is recommended in pregnancy. Hemoglobinopathy screening is recommended for all pregnant women with testing of mean corpuscular volume, mean corpuscular hemoglobin, ferritin, and hemoglobin analysis (Chap. 103). Hemoglobinopathies can be associated with increased maternal and fetal morbidity and mortality, with sickle cell disease as a particularly high-risk entity in pregnancy. Management is tailored to the specific hemoglobinopathy and is generally the same for both pregnant and nonpregnant women. Prenatal diagnosis of hemoglobinopathies in the fetus is readily available and should be discussed with prospective parents either prior to or early in pregnancy.

PART 19 Consultative Medicine Thrombocytopenia occurs in 5–10% of pregnancies. The majority of cases are benign gestational thrombocytopenias, but the differential diagnosis should include immune thrombocytopenia (Chap. 120), preeclampsia, and thrombotic thrombocytopenic purpura. Benign gestational thrombocytopenia is unlikely if the platelet count is $<100,000/\mu\text{L}$.

■ ■ **DEEP VENOUS THROMBOSIS AND**

PULMONARY EMBOLISM (See also Chap. 290) Pregnancy is associated with venous stasis, endothelial injury, and a hypercoagulable state. During pregnancy, circulating coagulation factors II, VII, VIII, IX, X, and XII, fibrinogen, and von Willebrand factor increase, and protein S and antithrombin III decrease. Inherited thrombophilias and the presence of antiphospholipid antibodies increase the risk of venous thromboembolism (VTE) in pregnancy and often require prophylactic anticoagulation during pregnancy and the postpartum period to mitigate risk. Deep venous thrombosis (DVT) or pulmonary embolism (PE) occurs in about

1 in 500 pregnancies, with the highest risk in the postpartum state. In general, all diagnostic and therapeutic modalities afforded to the nonpregnant patient should be utilized in pregnancy.

TREATMENT Venous Thromboembolism Aggressive diagnosis and management of suspected DVT or PE optimize outcomes for both patient and fetus. Anticoagulant therapy with low-molecular-

weight heparin (LMWH) or unfractionated heparin is indicated in pregnant people with VTE. Anticoagulants increase the risk of epidural hematoma in the setting of neuraxial analgesia (e.g., epidural or spinal anesthesia) in labor and must be withheld prior to placement. To ensure patient access to neuraxial analgesia in labor, prophylactic LMWH can be stopped 12 h before placement of an epidural catheter, whereas therapeutic LMWH can be discontinued for a full 24 h. Transition to unfractionated heparin as delivery approaches can shorten the time between anticoagulant administration and epidural placement. Unfractionated heparin can be used with an epidural catheter in place in those at highest risk of worsening thromboembolic disease.

■ ■ **NEOPLASIA** Cancer complicates ~1 in 1400 pregnancies. The four cancers that occur most commonly in pregnancy are cervical cancer, breast cancer, melanoma, and lymphoma. Also, cancer rates in pregnancy vary across the globe depending on local medical practices and exposures. In addition to cancers developing in other organs, gestational trophoblastic tumors can arise from the placenta. Pregnancy has relatively little or no impact on the natural history of malignancies, despite the hormonal influences. People with a history of active or treated hormonally responsive breast cancer who choose to pursue pregnancy have similar rates of cancer-related events as those who do not. Spread of the cancer to the fetus (so-called vertical transmission) is exceedingly rare. However, managing cancer in a pregnant person is complex, with competing interests for mother and fetus. Generally, the management that optimizes maternal physiology is also best for the fetus. The best way to approach management of a pregnant woman with cancer is to ask, “What would one do in this clinical situation if she was not pregnant? Then, which, if any, aspect of those plans needs to be modified because she is pregnant?”

TREATMENT

Malignancy Exposure of the developing fetus to therapeutic doses of ionizing radiation may cause adverse effects and is generally avoided during pregnancy. Chemotherapy is associated with adverse fetal effects, but the significance of these depends on the specific agent and gestational age. Cytotoxic chemotherapy should virtually never be given in the first trimester due to risk of spontaneous abortion or malformation. If avoiding chemotherapy during this vulnerable time period could compromise maternal health, patients should be counseled about the role of therapeutic abortion to avoid serious neonatal sequelae. A variety of single agents and combinations have been administered in the second and third trimesters, without a high frequency of toxic effects to the pregnancy or the fetus. Whether the association between chemotherapy and outcomes such as fetal growth restriction is due to the therapy or underlying malignancy is unknown. Literature supporting the short- and long-term neonatal safety of common agents is growing. For malignancies diagnosed closer to term or slowly progressive malignancies, delaying treatment until after delivery to avoid fetal exposure to chemotherapy may be desirable. If delaying therapy may compromise maternal prognosis, then treatment might be initiated after the first trimester of pregnancy with plans to deliver the fetus preterm to avoid excess cumulative exposure to chemotherapy. Neonatal prognosis is most closely linked to gestational age at delivery. Decisions regarding timing of delivery should contextualize this within the natural history of the disease, safety of the proposed treatment, and the person’s goals of care.

NEUROLOGIC DISORDERS

Neurologic complaints such as headaches or neuropathies are common in pregnancy, and differentiating bothersome symptoms from lifethreatening pathology is challenging (Chap. 437). While most complaints are benign, cerebrovascular accidents (CVAs) should be high on the differential diagnosis and evaluated with MRI without gadolinium or a head computed tomography (CT) in cases of suspected stroke. Noncontrast MRI is more sensitive than CT in identifying early and small infarcts and cerebral venous thrombosis. Exclusion of preeclampsia is important for any

patient presenting with a headache after 20 weeks of gestation with a low threshold to assess for CVA due to the comparatively high prevalence in this population. Headache in preeclampsia can be associated with the posterior reversible encephalopathy syndrome (PRES), which is on the spectrum of reversible cerebral vasoconstriction syndromes (RCVS) that can present in pregnancy or the postpartum period with neurologic complaints. Peripheral nerve disorders associated with pregnancy include

Bell's palsy (idiopathic facial paralysis) (Chap. 452), carpal tunnel syndrome (median nerve entrapment), or meralgia paresthetica (lateral femoral cutaneous nerve entrapment). Restless leg syndrome (RLS) is the most common peripheral nerve and movement disorder in pregnancy, affecting up to 20% of patients. If serum ferritin is low, oral iron supplementation is a first-line treatment option. Pregnancy is safe for most people with neurologic disorders, with management considerations focusing on medication safety, the impact of pregnancy on the disease, and potential neonatal consequences. For those with epilepsy planning pregnancy, lamotrigine and levetiracetam are first-line monotherapies due to the abundance of safety data. Valproate is known to be associated with congenital malformations and should be discontinued in favor of another medication for people planning to conceive. Folic acid supplementation of 4 mg daily is recommended for those taking antiepileptic drugs (AEDs). Escalating doses of AEDs may be required due to increased clearance in pregnancy and guided by monthly monitoring of AED levels. Patients with preexisting multiple sclerosis (Chap. 455) experience a gradual decrease in the risk of relapses as pregnancy progresses and, conversely, an increase in attack risk during the postpartum period. Prior to conception, disease-modifying therapies (DMTs) should be used to gain control of the disease. DMTs are typically withheld in pregnancy due to the decreased risk of relapse alongside limited neonatal safety data. Relapses should be treated with glucocorticoids, which may be given prophylactically after birth to reduce the risk of postpartum relapse. Finally, certain tumors, particularly pituitary adenoma (Chap. 392) and meningioma, may manifest during pregnancy because of accelerated growth, possibly driven by hormonal factors. Neuroimaging with noncontrast MRI may be required for women with a history of central nervous system (CNS) tumors to facilitate neuraxial analgesia.

GASTROINTESTINAL AND LIVER DISEASE Up to 90% of pregnant people experience nausea and vomiting during the first trimester of pregnancy. Hyperemesis gravidarum (HG) is a severe form that prevents adequate fluid and nutritional intake and may require hospitalization to prevent dehydration and malnutrition. GDF15, which is produced by the placenta and is known to suppress appetite, may be involved in the pathogenesis of HG. Thiamine and folate supplementation and monitoring of electrolytes for evidence of refeeding syndrome should be considered in severe cases with evaluation for supplemental enteral nutrition in refractory disease. Exacerbation of inflammatory bowel disease is common, and medical management, including the use of anti-tumor necrosis factor agents, parallels the nonpregnant state (Chap. 337). Pregnancy is a risk factor for development or worsening of gallbladder disease such as cholelithiasis. This aggravation may be due to pregnancy-induced alteration in the metabolism of bile and fatty acids. Intrahepatic cholestasis of pregnancy is generally a third-trimester event presenting with profound pruritus and confirmed with an elevated level of bile acids with or without transaminitis. The association between cholestasis and stillbirth merits increased fetal surveillance and delivery before term. Symptoms can be improved with the use of ursodiol. Acute fatty liver is a rare complication of pregnancy on the spectrum with HELLP syndrome and preeclampsia. Acute fatty liver of pregnancy is generally distinguished by markedly increased serum levels of bilirubin and ammonia and by hypoglycemia. Management of acute fatty

liver of pregnancy includes delivery accompanied by supportive care. Most people recover within 7–10 days after delivery, but reports of fulminant liver failure requiring transplant underscore the importance of prompt diagnosis and management. The association between acute fatty liver in pregnancy and long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency in the fetus inform the recommendation for close monitoring in the newborn with consideration of genetic testing. All pregnant people should be screened for hepatitis B virus with HBsAg testing and hepatitis C virus (Chap. 350). All infants receive hepatitis B vaccine, but infants born to mothers who are carriers of hepatitis B surface antigen should also receive hepatitis B immune

globulin as soon after birth as possible to decrease the risk of vertical transmission. The presence of the hepatitis B E antigen in the mother and high viral load increase the risk of vertical transmission. Strategies to decrease vertical transmission of hepatitis C are limited to avoiding procedures (i.e., amniocentesis) that increase the risk. Postpartum referral to a specialist for consideration of potentially curative therapy is indicated.

INFECTIONS ■ ■ BACTERIAL INFECTIONS All pregnant patients are screened prenatally for syphilis, gonorrhea, and chlamydial infections, and the detection of any of these should result in prompt evaluation and treatment (Chaps. 161, 187, and 194). Other than bacterial vaginosis, the most common bacterial infections during pregnancy involve the urinary tract (Chap. 140). All pregnant people should be screened with a urine culture for asymptomatic bacteriuria at the first prenatal visit. Pregnancy is an indication for treatment of asymptomatic bacteriuria to avoid pyelonephritis. Progesterone-mediated ureteral and bladder smooth muscle relaxation, coupled with compression effects of the enlarging uterus, promote stasis and increase the risk of these conditions. Pregnant women who develop pyelonephritis should be treated with inpatient IV antibiotic administration due to the elevated risk of urosepsis and acute respiratory distress syndrome in pregnancy-associated pyelonephritis. Pregnant people with recurrent urinary tract infections or one episode of pyelonephritis should receive daily antibiotic suppressive treatment throughout the remainder of their pregnancy. Options for suppressive treatment include nitrofurantoin (50 or 100 mg at bedtime) or cephalexin (250 or 500 mg at bedtime). **CHAPTER 491 Medical Disorders During Pregnancy ■ ■ VIRAL INFECTIONS** All pregnant people should be screened for hepatitis B virus, hepatitis C virus, and HIV as well as immunity to rubella and varicella. Screening for varicella immunity begins with obtaining a history of varicella immunization or infection. Testing for antibodies to varicella is reserved for cases where there is no history of prior immunization or infection, because the available varicella antibody test has low sensitivity and does not reliably detect antibodies in people who have been immunized. Influenza (See also Chap. 206) Pregnant people with influenza are at increased risk of serious complications and death. All people who are pregnant or plan to become pregnant in the near future should receive inactivated influenza vaccine. The prompt initiation of antiviral treatment is recommended for pregnant people in whom influenza is suspected. Treatment can be reconsidered once the results of high-sensitivity tests are available. Prompt initiation of treatment lowers the risk of admission to an intensive care unit and death. COVID-19 Pregnancy is a risk factor for severe COVID-19 infection. All unvaccinated people planning pregnancy or who are pregnant should receive a COVID-19 vaccine. Cytomegalovirus Infection The most common cause of congenital viral infection in the United States is cytomegalovirus (CMV) (Chap. 200). As many as 50–90% of women of childbearing age have antibodies to CMV, but only rarely does CMV reactivation result in neonatal infection. More commonly, primary CMV infection during pregnancy creates a risk of congenital CMV. No currently

accepted treatment of CMV infection during pregnancy has been demonstrated to protect the fetus effectively. Severe CMV disease in the newborn is characterized most often by petechiae, hepatosplenomegaly, and jaundice. Chorioretinitis, microcephaly, intracranial calcifications, hepatitis, hemolytic anemia, and purpura may also develop. CNS involvement can result in the development of psychomotor, ocular, auditory, and dental abnormalities over time. People with a primary CMV infection should delay conception for 6 months. Herpesvirus Infection (See also Chap. 197) The acquisition of genital herpes during pregnancy is associated with spontaneous

abortion, prematurity, and congenital and neonatal herpes. Disseminated neonatal herpes carries with it high mortality and morbidity rates from CNS involvement. A cohort study of pregnant people without evidence of previous herpesvirus infection demonstrated that ~2% acquired a new herpesvirus infection during the pregnancy and ~60% of the newly infected women had no clinical symptoms. The risk of transmission was increased in those with infections closer to delivery. The risk of active genital herpes lesions at term can be reduced by prescribing acyclovir (400 mg three times daily) for the last 4 weeks of pregnancy to all people who had an episode of genital herpes during the pregnancy. Those with active genital herpes lesions at the time of presentation in labor should be delivered by cesarean section.

Rubella (See also Chap. 212) Rubella virus is a known teratogen; first-trimester rubella carries a high risk of fetal malformations, although the risk significantly decreases later in pregnancy. Congenital rubella infection may be diagnosed by percutaneous umbilical-blood sampling with the detection of IgM antibodies in fetal blood. All pregnant people or those considering pregnancy should be tested for their immune status to rubella. Parvovirus Infection (See also Chap. 202) Infection with human parvovirus B19 may occur during pregnancy with the possibility of fetal transmission in the absence of immunity. It rarely causes significant maternal sequelae but can lead to erythroid aplasia in the fetus with resultant anemia, fetal hydrops, and death. Management includes screening for fetal anemia with Doppler assessment of the middle cerebral artery and consideration of intrauterine transfusion of red blood cells to the fetus to avoid the physiologic consequences of anemia while awaiting recovery of the fetal bone marrow. PART 19 Consultative Medicine HIV Infection (See also Chap. 208) The predominant cause of HIV infection in children is transmission of the virus from mother to newborn during the perinatal period. All pregnant women should be screened for HIV infection. Factors that increase the risk of mother-to-newborn transmission include high maternal viral load, low maternal CD4+ T-cell count, prolonged labor, prolonged duration of membrane rupture, and the presence of other genital tract infections, such as syphilis or herpes. Antiretroviral therapy (ART) has decreased the rate of perinatal transmission from 20% to ~1%. For those receiving antepartum ART, viral load guides the decision for vaginal versus cesarean delivery and need for adjunct intrapartum zidovudine. People with an undetectable viral load are at the lowest risk of transmission and require no additional therapy, whereas those without antepartum ART exposure or with viral loads >1000 copies/mL at delivery require IV zidovudine and a prelabor cesarean delivery, typically scheduled at 38 weeks. Cesarean delivery should be reserved for obstetric indications for women with ≥ 50 but ≤ 1000 copies/mL, and intrapartum zidovudine can be considered. Zika Virus Zika virus (ZIKV) can be transmitted from mother to fetus throughout gestation and often results in severe microcephaly, CNS malformations, and fetal death. Symptomatic pregnant people with relevant epidemiologic exposure within 2 weeks of symptom onset should have serum and urine tested for ZIKV and dengue nucleic acids by nucleic acid amplification test and IgM serology. Sequential obstetrical

ultrasound is recommended to assess for fetal growth and anomalies. Couples considering pregnancy should avoid travel to areas with known mosquito transmission of ZIKV. ■

■ **VACCINATIONS** (See also Chap. 129) For rubella-nonimmune individuals contemplating pregnancy, measles-mumps-rubella vaccine should be administered, ideally at least 3 months prior to conception, but otherwise in the immediate postpartum period. All pregnant people should be vaccinated against influenza and COVID-19. Administration of one dose of the tetanus, diphtheria, and pertussis (Tdap) vaccine between 27 and 36 weeks of gestation is recommended to promote maternal IgG production and reduce the risk of neonatal pertussis due to transplacental passage of IgG.

MATERNAL MORTALITY Maternal death is defined as death occurring during pregnancy or within 42 days of completion of pregnancy from a cause related to or aggravated by pregnancy, but not due to accident or incidental causes. The maternal mortality rate is the number of maternal deaths per 100,000 live births. From 1935 to 2007, the U.S. maternal mortality rate decreased from nearly 600/100,000 births to 12.7/100,000 births, rising thereafter. In 2021, the U.S. maternal mortality rate was 32.9/100,000 births. An increasingly complex patient population, with multiple comorbidities, and the COVID-19 pandemic likely contributed to the high rate of maternal death in 2021. There are significant racial and ethnic disparities in the maternal mortality rate, with a nearly fourfold increased risk of death for non-Hispanic black women compared to non-Hispanic white women (69.9 vs 26.6 deaths per 100,000 live births, respectively) (Chap. 11). Women over 40 years of age had a maternal mortality rate of 139 per 100,000 live births. Pregnancy-related death is defined as the death of a person while pregnant or within 1 year of the end of pregnancy from any cause related to or aggravated by pregnancy. Cardiovascular disease, including cardiomyopathy, accounted for nearly a third of pregnancy-related deaths from 2014 to 2017 followed by infection, noncardiovascular medical conditions, hemorrhage, and thrombotic events. The relative contribution of medical disease to pregnancy-related death, coupled with knowledge that one in three pregnancy-related deaths occur 1 week to 1 year after delivery, highlights the role of the specialist in internal medicine in reducing maternal mortality. In some countries in sub-Saharan Africa and southern Asia, the maternal mortality rate is >500/100,000 live births. The most common causes of maternal death in these countries are maternal hemorrhage, hypertensive disorders, infection, obstructed labor, and complications from unsafe pregnancy termination. The health interventions that have the greatest impact on maternal health include improving the following components of the health system: (1) access to contraceptive services in order to space births and limit total family size; (2) access to safe pregnancy termination; (3) presence of trained birth attendants at all deliveries; and (4) transportation to emergency obstetrical centers that can provide intensive medical and surgical services, including cesarean delivery. Maternal death is a global public health tragedy that could be mitigated with the application of modest resources.

SUMMARY With improved diagnostic and therapeutic modalities as well as advances in the treatment of infertility, more patients with serious medical complications will be seeking to become pregnant and will require complex obstetric care. Improved outcomes of pregnancy in these people will be best attained by a multidisciplinary team of internists, maternal-fetal medicine (high-risk obstetrics) specialists, pediatricians, and anesthesiologists assembled to counsel these patients about the risks of pregnancy and to optimize interconception care. The importance of preconception counseling and the impact of events of pregnancy on lifelong disease cannot be overstated. It is the responsibility of all physicians caring for women in the reproductive age group to assess their patients' reproductive plans as part of their overall health evaluation and to integrate pregnancy-related diagnoses into their assessment of future risk for cardiovascular

disease. ■ ■FURTHER READING Crisafulli F et al: Variations of C3 and C4 before and during pregnancy in systemic lupus erythematosus: Association with disease flares and obstetric outcomes. J Rheumatol 50:1296, 2023. Ford ND et al: Hypertensive disorders in pregnancy and mortality at delivery hospitalization-United States, 2017-2019. Morb Mortal Week Report 71:585, 2022. Fu J et al: Increased risk of major congenital malformations in early pregnancy uses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: A meta-analysis. Diabetes Metab Res Rev 37:e3453, 2021. Hoyert DL: Maternal mortality rates in the United States, 2021. NCHS Health E-Stats. 2023. DOI: <https://dx.doi.org/10.15620/cdc:124678>.

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